

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



B1
#6

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, C07K 14/72	A2	(11) International Publication Number: WO 00/31258	(43) International Publication Date: 2 June 2000 (02.06.00)
---	----	---	--

(21) International Application Number: PCT/US99/23687

09/416,760 12 October 1999 (12.10.99) US

(22) International Filing Date: 13 October 1999 (13.10.99)

(30) Priority Data:

60/109,213	20 November 1998 (20.11.98)	US
60/120,416	16 February 1999 (16.02.99)	US
60/121,852	26 February 1999 (26.02.99)	US
60/123,946	12 March 1999 (12.03.99)	US
60/123,949	12 March 1999 (12.03.99)	US
60/136,436	28 May 1999 (28.05.99)	US
60/136,437	28 May 1999 (28.05.99)	US
60/136,439	28 May 1999 (28.05.99)	US
60/136,567	28 May 1999 (28.05.99)	US
60/137,127	28 May 1999 (28.05.99)	US
60/137,131	28 May 1999 (28.05.99)	US
60/141,448	29 June 1999 (29.06.99)	US
60/156,653	29 September 1999 (29.09.99)	US
60/156,633	29 September 1999 (29.09.99)	US
60/156,555	29 September 1999 (29.09.99)	US
60/156,634	29 September 1999 (29.09.99)	US
60/157,280	1 October 1999 (01.10.99)	US
60/157,294	1 October 1999 (01.10.99)	US
60/157,281	1 October 1999 (01.10.99)	US
60/157,293	1 October 1999 (01.10.99)	US
60/157,282	1 October 1999 (01.10.99)	US
09/417,044	12 October 1999 (12.10.99)	US

(71) Applicant (for all designated States except US): ARENA PHARMACEUTICALS, INC. [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CHEN, Ruoping [CN/US]; 5296 Timber Branch Way, San Diego, CA 92130 (US). DANG, Huong, T. [US/US]; 5352 Oak Park Drive, San Diego, CA 92105 (US). LIAW, Chen, W. [US/US]; 7668 Salix Place, San Diego, CA 92129 (US). LIN, I-Lin [-/US]; 8291-7 Gold Coast Drive, San Diego, CA 92126 (US).

(74) Agents: MILLER, Suzanne, E. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris LLP, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: HUMAN ORPHAN G PROTEIN-COUPLED RECEPTORS

(57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to endogenous, human orphan G protein-coupled receptors.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

HUMAN ORPHAN G PROTEIN-COUPLED RECEPTORS

This patent document claims priority benefit of each of the following applications, all filed with the United States Patent and Trademark Office via U.S. Express Mail on the indicated filing dates: U.S. Provisional Number 60/121,852, filed February 26, 1999 claiming the benefit of U.S. Provisional Number 60/109,213, filed November 20, 1998; U.S. Provisional Number 60/120,416, filed February 16, 1999; U.S. Provisional Number 60/123,946, filed March 12, 1999; U.S. Provisional Number 60/123,949, filed March 12, 1999; U.S. Provisional Number 60/136,436, filed May 28, 1999; U.S. Provisional Number 60/136,439, filed May 28, 1999; U.S. Provisional Number 60/136,567, filed May 28, 1999; U.S. Provisional Number 60/137,127, filed May 28, 1999; U.S. Provisional Number 60/137,131, filed May 28, 1999; U.S. Provisional Number 141,448, filed June 29, 1999 claiming priority from U.S. Provisional Number 60/136,437, filed May 28, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number CHN10-1), filed September 29, 1999; U.S. Provisional Number 60/156,333, filed September 29, 1999; U.S. Provisional Number 60/156,555, filed September 29, 1999; U.S. Provisional Number 60/156,634, filed September 29, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number RUP6-1), filed October 1, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number RUP7-1), filed October 1, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number CHN6-1), filed October 1, 1999; U.S. Provisional

- 2 -

Number _____ (Arena Pharmaceuticals, Inc. docket number RUP5-1), filed October 1, 1999; U.S. Provisional Number _____ (Arena Pharmaceuticals, Inc. docket number CHN9-1), filed October 1, 1999. This patent document is related to U.S. Serial Number 09/170,496 filed October 13, 1998, and U.S. Serial Number unknown (Woodcock 5 Washburn Kurtz Mackiewicz & Norris, LLP docket number AREN-0054) filed on October 12, 1999 (via U.S. Express Mail) both being incorporated herein by reference. This patent document also is related to U.S. Serial No. 09/364,425; filed July 30, 1999, which is incorporated by reference in its entirety. This application also claims priority to U.S. Serial Number _____ (Woodcock, Washburn, Kurtz, Makiewicz & Norris, LLP 10 docket number AREN-0050), filed on October 12, 1999 (via U.S. Express Mail), incorporated by reference herein in its entirety. Each of the foregoing applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, 15 and more particularly to endogenous, orphan, human G protein-coupled receptors ("GPCRs").

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) 20 class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2% or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified

- 3 -

are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed. This distinction is not merely semantic, particularly in the case of GPCRs. Thus, the orphan GPCRs are to the pharmaceutical industry what gold was to California in the late 19th century – an opportunity to drive growth, expansion, enhancement and development.

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmembrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It

- 4 -

has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.*, that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response. A receptor may be stabilized in an active state by an endogenous ligand or a compound such as a drug.

SUMMARY OF THE INVENTION

Disclosed herein are human endogenous orphan G protein-coupled receptors.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B provide reference "grids" for certain dot-blot analyses provided herein (see also, Figure 2A and 2B, respectively).

Figures 2A and 2B provide reproductions of the results of certain dot-blot analyses resulting from hCHN3 and hCHN8, respectively (see also, Figures 1A and 1B, respectively).

Figure 3 provides a reproduction of the results of RT-PCR analysis of hRUP3.

Figure 4 provides a reproduction of the results of RT-PCR analysis of hRUP4.

Figure 5 provides a reproduction of the results of RT-PCR analysis of hRUP6.

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of 5 terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AMINO ACID ABBREVIATIONS used herein are set out in Table 1:

10	TABLE 1		
	ALANINE	ALA	A
	ARGININE	ARG	R
	ASPARAGINE	ASN	N
	ASPARTIC ACID	ASP	D
15	CYSTEINE	CYS	C
	GLUTAMIC ACID	GLU	E
	GLUTAMINE	GLN	Q
	GLYCINE	GLY	G
	HISTIDINE	HIS	H
20	ISOLEUCINE	ILE	I
	LEUCINE	LEU	L
	LYSINE	LYS	K
	METHIONINE	MET	M
	PHENYLALANINE	PHE	F
25	PROLINE	PRO	P
	SERINE	SER	S
	THREONINE	THR	T
	TRYPTOPHAN	TRP	W
	TYROSINE	TYR	Y
30	VALINE	VAL	V

COMPOSITION means a material comprising at least one component.

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a

- 6 -

human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector 5 incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention 10 disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring 15 molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid 20 is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

VECTOR sin reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

- 7 -

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

Identification of Human GPCRs

5 The efforts of the Human Genome project have led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins.

10 Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLAST™ search of the EST database. Table A, below,

15 lists the disclosed endogenous orphan GPCRs along with a GPCR's respective homologous GPCR:

TABLE A

Disclosed	Accession	Open Reading	Per Cent	Reference To
Human	Number	Frame	Homology	Homologous
Orphan	Identified	(Base Pairs)	To Designated	GPCR
GPCRs			GPCR	(Accession No.)
hARE-3	AL033379	1,260 bp	52.3% LPA-R	U92642
hARE-4	AC006087	1,119 bp	36% P2Y5	AF000546

- 8 -

	hARE-5	AC006255	1,104 bp	32% <i>Oryzias</i>	D43633
				<i>latipes</i>	
	hGPR27	AA775870	1,128 bp		
	hARE-1	AI090920	999 bp	43%	D13626
				KIAA0001	
5	hARE-2	AA359504	1,122 bp	53% GPR27	
	hPPR1	H67224	1,053 bp	39% EB11	L31581
	hG2A	AA754702	1,113 bp	31% GPR4	L36148
	hRUP3	AL035423	1,005 bp	30%	2133653
				<i>Drosophila</i>	
				<i>melanogaster</i>	
	hRUP4	AI307658	1,296 bp	32% pNPGPR	NP_004876
				28% and 29 %	AAC41276
				<i>Zebra fish</i> Ya	and
				and Yb,	AAB94616
				respectively	
	hRUP5	AC005849	1,413 bp	25% DEZ	Q99788
				23% FMLPR	P21462
10	hRUP6	AC005871	1,245 bp	48% GPR66	NP_006047
	hRUP7	AC007922	1,173 bp	43% H3R	AF140538
	hCHN3	EST 36581	1,113 bp	53% GPR27	
	hCHN4	AA804531	1,077 bp	32% thrombin	4503637
	hCHN6	EST 2134670	1,503 bp	36% edg-1	NP_001391
15	hCHN8	EST 764455	1,029 bp	47%	D13626
				KIAA0001	
	hCHN9	EST 1541536	1,077 bp	41% LTB4R	NM_000752
	hCHN10	EST 1365839	1,055 bp	35% P2Y	NM_002563

Receptor homology is useful in terms of gaining an appreciation of a role of the disclosed receptors within the human body. Additionally, such homology can provide insight as to possible endogenous ligand(s) that may be natural activators for the disclosed orphan GPCRs.

B. Receptor Screening

Techniques have become more readily available over the past few years for

- 9 -

endogenous-ligand identification (this, primarily, for the purpose of providing a means of conducting receptor-binding assays that require a receptor's endogenous ligand) because the traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

As is known in the art, GPCRs can be "active" in their endogenous state even without the binding of the receptor's endogenous ligand thereto. Such naturally-active receptors can be screened for the direct identification (*i.e.*, without the need for the receptor's endogenous ligand) of, in particular, inverse agonists. Alternatively, the receptor can be "activated" via, *e.g.*, mutation of the receptor to establish a non-endogenous version of the receptor that is active in the absence of the receptor's endogenous ligand.

Screening candidate compounds against an endogenous or non-endogenous, constitutively activated version of the human orphan GPCRs disclosed herein can provide for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of human orphan GPCRs disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR typically nears the TM6/IC3 interface (such proline residue appears to be quite conserved). By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

C. Disease/Disorder Identification and/or Selection

Preferably, the DNA sequence of the human orphan GPCR can be used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated

with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

D. Screening of Candidate Compounds

5 1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active (i.e., active in the absence of endogenous ligand binding thereto), it binds to a G protein (e.g., Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes
10 deactivated. However, constitutively activated receptors continue to exchange GDP to GTP.

A non-hydrolyzable analog of GTP, [³⁵S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that [³⁵S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and
15 available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

20 Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (i.e., an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the

receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. *Gs and Gi.*

Gs stimulates the enzyme adenylyl cyclase. Gi (and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple the Gi (or Go) protein are associated with decreased cellular levels of cAMP. *See, generally, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992).* Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) which then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as β -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

Go and Gq.

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP_2 , releasing two intracellular messengers: 5 diacylglycerol (DAG) and inistol 1,4,5-triphoisphate (IP_3). Increased accumulation of IP_3 is associated with activation of Gq- and Go-associated receptors. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP_3 accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go- 10 associated receptor (*i.e.*, such a compound would decrease the levels of IP_3). Gq-associated receptors can also been examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will 15 evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activated orphan GPCR, or a non-endogenous, constitutively activated orphan GPCR, for screening of candidate compounds 20 for the direct identification of inverse agonists, agonists and partial agonists provides a unique challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, it is often useful that an approach be utilized that can enhance the signal obtained by the activated receptor. A preferred approach is the use of a GPCR Fusion Protein.

- 14 -

Generally, once it is determined that a GPCR is or has been constitutively activated, using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques, although the GPCR Fusion Protein can also be (and preferably is) used with an endogenous, constitutively activated GPCR. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is important preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the GPCR is upstream of the G protein sequence) and that the "stop" codon of

- 15 -

the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

E. Other Utility

Although a preferred use of the human orphan GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. The value in human orphan GPCRs is that its utility as a research tool is enhanced in that by determining the location(s) of such receptors within the body, the GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified.

Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. Unless otherwise indicated below, all nucleic acid sequences for the disclosed endogenous orphan human GPCRs have been sequenced and verified. For purposes of equivalent receptors, those of ordinary skill in the art will readily appreciate that conservative substitutions can be made to the disclosed sequences to obtain a functionally equivalent receptor.

Example 1

ENDOGENOUS HUMAN GPCRS

1. Identification of Human GPCRs

Several of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank database information. While searching the database, the following cDNA clones were identified as evidenced below.

Disclosed	Accession	Complete DNA	Open Reading	Nucleic Acid	Amino
Human	Number	Sequence	Frame	SEQ.ID.	Acid
Orphan		(Base Pairs)	(Base Pairs)	NO.	SEQ.ID.
GPCRs					NO.

- 17 -

	hARE-3	AL033379	111,389 bp	1,260 bp	1	2
	hARE-4	AC006087	226,925 bp	1,119 bp	3	4
	hARE-5	AC006255	127,605 bp	1,104 bp	5	6
	hRUP3	AL035423	140,094 bp	1,005 bp	7	8
5	hRUP5	AC005849	169,144 bp	1,413 bp	9	10
	hRUP6	AC005871	218,807 bp	1,245 bp	11	12
	hRUP7	AC007922	158,858 bp	1,173 bp	13	14

Other disclosed endogenous human GPCRs were identified by conducting a BLAST search of EST database (dbest) using the following EST clones as query sequences. The 10 following EST clones identified were then used as a probe to screen a human genomic library.

	Disclosed	Query	EST Clone/ Accession No.	Open Reading Frame	Nucleic Acid SEQ.ID.NO.	Amino Acid SEQ.ID.NO.
	Human Orphan	(Sequence)	Identified	(Base Pairs)		
15	GPCRs hGPCR27	Mouse	AA775870	1,125 bp	15	16
	hARE-1	GPCR27 TDAG	1689643	999 bp	17	18
	hARE-2	GPCR27	A1090920 68530	1,122 bp	19	20
	hPPR1	Bovine	AA359504 238667	1,053 bp	21	22
20	hG2A	PPR1 Mouse	H67224 <i>See Example 2(a),</i>	1,113 bp	23	24
		1179426	<i>below</i>			

- 18 -

	hCHN3	N.A.	EST 36581	1,113 bp	25	26
	hCHN4	TDAG	(full length) 1184934	1,077 bp	27	28
	hCHN6	N.A.	AA804531 EST 2134670	1,503 bp	29	30
	hCHN8	K1AA0001	(full length) EST 764455	1,029 bp	31	32
5	hCHN 9	1365839	EST 1541536	1,077 bp	33	34
	hCHN10	Mouse EST	Human 1365839	1,005 bp	35	36
	hRUP4	1365839 N.A.	A1307658	1,296 bp	37	38
		N.A. = "not applicable".				

2. Full Length Cloning

10 a. hG2A (Seq. Id. Nos. 23 & 24)

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all but three amino acid hG2A coding sequences. The 5' end of this coding sequence was obtained by using 5'RACE™, and the template for PCR was Clontech's Human Spleen Marathon-ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A
 15 cDNA specific primers for the first and second round PCR as shown in SEQ.ID.NO.: 39 and SEQ.ID.NO.:40 as follows:

5'-CTGTGTACAGCAGTTCGCAGAGTG-3' (SEQ.ID.NO.: 39; 1st round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3' (SEQ.ID.NO.: 40; second round PCR).

PCR was performed using Advantage™ GC Polymcrase Kit (Clontech; manufacturing
 20 instructions will be followed), at 94°C for 30 sec followed by 5 cycles of 94°C for 5 sec and 72°C for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions will be followed) and

- 19 -

the sequence was compared with the presented sequence. Expression of the human G2A will be detected by probing an RNA dot blot (Clontech; manufacturer instructions will be followed) with the P³²-labeled fragment.

b. hCHN9 (Seq. Id. Nos. 33 & 34)

5 Sequencing of the EST clone 1541536 indicated that hCHN9 is a partial cDNA clone having only an initiation codon; *i.e.*, the termination codon was missing. When hCHN9 was used to "blast" against the data base (nr), the 3' sequence of hCHN9 was 100% homologous to the 5' untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with hCHN9 coding sequence. To 10 determine whether the 5' untranslated region of LTB4R cDNA was the 3' sequence of hCHN9, PCR was performed using primers based upon the 5' sequence flanking the initiation codon found in hCHN9 and the 3' sequence around the termination codon found in the LTB4R 5' untranslated region. The 5' primer sequence utilized was as follows:

5'-CCCGAATTCCTGCTTGCTCCCAGCTTGGCCC-3' (SEQ.ID.NO.: 41; sense) and

15 5'-TGTGGATCCTGCTGTCAAAGGTCCCATTCGGG-3' (SEQ.ID.NO.: 42; antisense).

PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72 °C for 1 min and 10 sec. A 1.1kb fragment consistent with the predicted size was 20 obtained from PCR. This PCR fragment was subcloned into pCMV (*see below*) and sequenced (*see*, SEQ.ID.NO.: 33).

c. hRUP 4 (Seq. Id. Nos. 37 & 38)

The full length hRUP4 was cloned by RT-PCR with human brain cDNA (Clontech)

as templates:

5'-TCACAATGCTAGGTGTGGTC-3' (SEQ.ID.NO.: 43; sense) and

5'-TGCATAGACAATGGGATTACAG-3' (SEQ.ID.NO.: 44; antisense).

PCR was performed using TaqPlus™ Precision™ polymerase (Stratagene; manufacturing instructions will be followed) by the following cycles: 94°C for 2 min; 94°C 30 sec; 55°C for 30 sec, 72°C for 45 sec, and 72°C for 10 min. Cycles 2 through 4 were repeated 30 times.

The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and sequenced using the T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

5'-TCACAATGCTAGGTGTGGTCTGGCTGGTGGCAGTCATCGTAGGATCACCCATGTGGCAC
 15 GTGCAACAACCTGAGATCAAATATGACTTCCTATATGAAAAGGAACACATCTGCTGCTTAGAA
 GAGTGGACCAGCCCTGTGCACCAGAAGATCTACACCACCTTCATCCTTGTCATCCTCTTCCTCC
 TGCCTCTTATGGTGATGCTTATTCTGTACGTAAAATTGGTTATGAACTTTGGATAAAGAAAAGA
 GTTGGGGATGGTTCAGTGCTTCGAACTATTCATGGAAAAGAAATGTCCAAAATAGCCAGGAAG
 AAGAAACGAGCTGTCAATTATGATGGTGACAGTGGTGGCTCTCTTTGCTGTGTGCTGGGCACCA
 20 TTCCATGTTGTCCATATGATGATTGAATACAGTAATTTGAAAAGGAATATGATGATGTCACA
 ATCAAGATGATTTTGGCTATCGTGCAAATTATTGGATTTCCAACCTCCATCTGTAATCCCATTG
 TCTATGCA-3' (SEQ.ID.NO.: 45)

Based on the above sequence, two sense oligonucleotide primer sets:

5'-CTGCTTAGAAGAGTGGACCAG-3' (SEQ.ID.NO.: 46; oligo 1),

25 5'-CTGTGCACCAGAAGATCTACAC-3' (SEQ.ID.NO.: 47; oligo 2)

and two antisense oligonucleotide primer sets:

5'-CAAGGATGAAGGTGGTGTAGA-3' (SEQ.ID.NO.: 48; oligo 3)

5'-GTGTAGATCTTCTGGTGCACAGG-3' (SEQ.ID.NO.: 49; oligo 4)

were used for 3'- and 5'-race PCR with a human brain Marathon-Ready™ cDNA (Clontech,

- 21 -

Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers. The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop codon. The 5' RACE product contained an incomplete 5' end; *i.e.*, the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC-3' (SEQ.ID.NO.: 50; oligo 5)

were used for the second round of 5' RACE PCR and the PCR products were analyzed as above. A third round of 5' RACE PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGGAATGCAGAAG-3' (SEQ.ID.NO.: 51; oligo 6) and

5'-GTGATGAGCAGGTCAGTCTGAGCGCCAAG-3' (SEQ.ID.NO.: 52; oligo 7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon ATG, and further round of 5' RACE PCR did not generate any more 5' sequence. The completed 5' sequence was confirmed by RT-PCR using sense primer

5'-GCAATGCAGGCGCTTAACATTAC-3' (SEQ.ID.NO.: 53; oligo 8)

and oligo 4, as primers and sequence analysis of the 650 bp PCR product generated from human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ.ID.NO.: 54; oligo 9)

and sequence analysis of the 670 bp PCR product generated from human brain and heart cDNA templates. (Clontech, Cat# 7404-1).

d. hRUP5 (Seq. Id. Nos. 9 & 10)

The full length hRUP5 was cloned by RT-PCR using a sense primer upstream from

ATG, the initiation codon (SEQ.ID.NO.: 55), and an antisense primer containing TCA as the stop codon (SEQ.ID.NO.: 56), which had the following sequences:

5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ.ID.NO.:55)

5'-TGCGTGTTCTGGACCCTCACGTG-3' (SEQ.ID.NO.: 56)

5 and human peripheral leukocyte cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 through step 4 repeated 30 times: 94°C for 30 sec; 94° for 15 sec; 69° for 40 sec; 72°C for 3 min; and 72°C for 6 min. A 1.4kb PCR fragment was isolated and cloned with the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA
10 Sequenase™ kit (Amsham). See, SEQ.ID.NO.: 9.

e. hRUP6 (Seq. Id. Nos. 11 & 12)

The full length hRUP6 was cloned by RT-PCR using primers:

5'-CAGGCCTTGGATTTTAATGTCAGGGATGG-3' (SEQ.ID.NO.: 57) and

5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 58);

15 and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50ul reaction by the following cycle: 94°C for 30sec; 94°C for 5 sec; 66°C for 40sec; 72°C for 2.5 sec and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen)
20 and completely sequenced (see, SEQ.ID.NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

f. hRUP7 (Seq. Id. Nos. 13 & 14)

The full length RUP7 was cloned by RT-PCR using primers:

5'-TGATGTGATGCCAGATACTAATAGCAC-3' (SEQ.ID.NO.: 59; sense) and

- 23 -

5'-CCTGATTCATTTAGGTGAGATTGAGAC-3' (SEQ.ID.NO.: 60; antisense)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following cycle with step 2 to step 4 repeated 30 times: 94°C for 2 minutes; 94°C for 15 seconds; 60°C for 20 seconds; 72°C for 2 minutes; 72°C for 10 minutes. A 1.25 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator™ kit (P.E. Biosystem). See, SEQ.ID.NO.: 13.

g. hARE-5 (Seq. Id. Nos. 5 & 6)

The full length hARE-5 was cloned by PCR using the hARE5 specific primers 10 5'-CAGCGCAGGGTGAAGCCTGAGAGC-3' SEQ.ID.NO.: 69 (sense, 5' of initiation codon ATG) and 5'-GGCACCTGCTGTGACCTGTGCAGG-3' SEQ.ID.NO.:70 (antisense, 3' of stop codon TGA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 96°C, 2 minutes; 96°C, 20 seconds; 58°C, 30 seconds; 72°C, 2 minutes; and 72°C, 10 minutes
15 A 1.1 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.:5) using the T7 DNA Sequenase™ kit (Amsham).

h. hARE-4 (Seq. Id. Nos.: 3 & 4)

The full length hARE-4 was cloned by PCR using the hARE-4 specific primers 5'-
20 CTGGTGTGCTCCATGGCATCCC-3' SEQ.ID.NO.:67 (sense, 5' of initiation codon ATG) and 5'-GTAAGCCTCCCAGAACGAGAGG-3' SEQ.ID.NO.: 68 (antisense, 3' of stop codon TGA) and human genomic DNA as template. Taq DNA polymerase (Stratagene) and 5% DMSO was used for the amplification by the following cycle with step 2 to step 3 repeated 35 times:

94°C, 3 minutes; 94°C, 30 seconds; 59°C, 2 minutes; 72°C, 10 minutes

A 1.12 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.:3) using the T7 DNA Sequenase™ kit (Amsham).

5 i. hARE-3 (Seq.Id.Nos.: 1 & 2)

The full length hARE-3 was cloned by PCR using the hARE-3 specific primers 5'-gatcaagcttCCATCCTACTGAAACCATGGTC-3' SEQ.ID.NO.:65 (sense, lower case nucleotides represent Hind III overhang, ATG as initiation codon) and 5'-gatcagarctCAGTTCCAATATTCACACCACCGTC-3' SEQ.ID.NO.:66 (antisense, lower case 10 nucleotides represent Xba I overhang, TCA as stop codon) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C, 3 minutes; 94°C, 1 minute; 55°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes.

A 1.3 Kb PCR fragment of predicated size was isolated and digested with Hind III 15 and Xba I, cloned into the pRC/CMV2 vector (Invitrogen) at the Hind III and Xba I sites and completely sequenced (SEQ.ID.NO.:1) using the T7 DNA Sequenase™ kit (Amsham).

 j. hRUP3 (Seq. Id. Nos.:7 & 8)

The full length hRUP3 was cloned by PCR using the hRUP3 specific primers 5'-GTCCTGCCACTTCGAGACATGG-3' SEQ.ID.NO.:71 (sense, ATG as initiation codon) and 5'-20 GAAACTTCTCTGCCCTTACCGTC-3' SEQ.ID.NO.:72 (antisense, 3' of stop codon TAA) and human genomic DNA as template. TaqPlus Precision™ DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C, 3 minutes; 94°C, 1 minute; 58°C, 1 minute; 72°C, 2 minutes; 72°C, 10 minutes

- 25 -

A 1.0 Kb PCR fragment of predicated size was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (SEQ.ID.NO.: 7) using the T7 DNA sequenase kit (Amsham).

Example 2

5 RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the 10 case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems - thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular 15 needs of the artisan. The general procedure for expression of the disclosed GPCRs is as follows.

On day one, 1×10^7 293T cells per 150mm plate were plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 20µg DNA (*e.g.*, pCMV vector; pCMV vector with receptor 20 cDNA, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120µl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B are admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture can be referred to as the "transfection mixture". Plated 293T cells are washed with 1XPBS, followed by addition of 10ml serum free DMEM.

2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO₂. The transfection mixture was then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO₂. After 72hr incubation, cells can then be harvested and utilized for analysis.

5 Example 3

TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRS

Several approaches can be used for determination of the tissue distribution of the GPCRs disclosed herein.

1. Dot-Blot Analysis

10 Using a commercially available human-tissue dot-blot format, endogenous orphan GPCRs were probed for a determination of the areas where such receptors are localized. cDNA fragments from the GPCRs of Example 1 (radiolabelled) were (or can be) used as the probe: radiolabeled probe was (or can be) generated using the complete receptor cDNA (excised from the vector) using a Prime-It II™ Random Primer Labeling Kit (Stratagene, 15 #300385), according to manufacturer's instructions. A human RNA Master Blot™ (Clontech, #7770-1) was hybridized with the endogenous human GPCR radiolabeled probe and washed under stringent conditions according manufacturer's instructions. The blot was exposed to Kodak BioMax™ Autoradiography film overnight at -80°C. Results are summarized for several receptors in Table B and C (*see* Figures 1A and 1B for a grid 20 identifying the various tissues and their locations, respectively). Exemplary dot-blot results are provided in Figure 2A and 2B for results derived using hCHN3 and hCHN8, respectively.

TABLE B

ORPHAN GPCR

Tissue Distribution
(highest levels, relative to other tissues in the dot-blot)

- 27 -

	hGPCR27	Fetal brain, Putamen, Pituitary gland, Caudate nucleus
	hARE-1	Spleen, Peripheral leukocytes, Fetal spleen
	hPPR1	Pituitary gland, Heart, salivary gland, Small intestine, Testis
	hRUP3	Pancreas
5	hCHN3	Fetal brain, Putamen, Occipital cortex
	hCHN9	Pancreas, Small intestine, Liver
	hCHN10	Kidney, Thryoid

TABLE C

ORPHAN GPCR		Tissue Distribution (highest levels, relative to other tissues in the dot-blot)
10	hARE-3	Cerebellum left, Cerebellum right, Testis, Accumbens
	hGPCR3	Corpus collusum, Caudate nucleus, Liver, Heart, Inter-Ventricular Septum
	hARE-2	Cerebellum left, Cerebellum right, Substantia
	hCHN8	Cerebellum left, Cerebellum right, Kidney, Lung

2. RT-PCR

15 a. hRUP3

To ascertain the tissue distribution of hRUP3 mRNA, RT-PCR was performed using hRUP3-specific primers and human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was utilized for the PCR reaction, using the following reaction cycles in a 40ul reaction: 94°C for 2 min; 94°C for 15 sec; 55°C for 30 20 sec; 72°C for 1 min; 72° C, for 10 min. Primers were as follows:

5'-GACAGGTACCTTGCCATCAAG-3' (SEQ.ID.NO.: 61; sense)

5'-CTGCACAATGCCAGTGATAAGG-3' (SEQ.ID.NO.: 62; antisense).

20ul of the reaction was loaded onto a 1% agarose gel; results are set forth in Figure 3.

- 28 -

As is supported by the data of Figure 3, of the 16 human tissues in the cDNA panel utilized (brain, colon, heart, kidney, lung, ovary, pancreas, placenta, prostate, skeleton, small intestine, spleen, testis, thymus leukocyte, and liver) a single hRUP3 band is evident only from the pancreas. Additional comparative analysis of the protein sequence of hRUP3 with 5 other GPCRs suggest that hRUP3 is related to GPCRs having small molecule endogenous ligand such that it is predicted that the endogenous ligand for hRUP3 is a small molecule.

b. hRUP4

RT-PCR was performed using hRUP4 oligo's 8 and 4 as primers and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase 10 (Stratagene) was used for the amplification in a 40ul reaction by the following cycles: 94°C for 30 seconds, 94°C for 10 seconds, 55°C for 30 seconds, 72°C for 2 minutes, and 72°C for 5 minutes with cycles 2 through 4 repeated 30 times.

20 μ l of the reaction were loaded on a 1% agarose gel to analyze the RT-PCR products, and hRUP4 mRNA was found expressed in many human tissues, with the strongest 15 expression in heart and kidney. (see, Figure 4). To confirm the authenticity of the PCR fragments, a 300 bp fragment derived from the 5' end of hRUP4 was used as a probe for the Southern Blot analysis. The probe was labeled with 32 P-dCTP using the Prime-It II™ Random Primer Labeling Kit (Stratagene) and purified using the ProbeQuant™ G-50 micro columns (Amersham). Hybridization was done overnight at 42° C following a 12 hr pre- 20 hybridization. The blot was finally washed at 65°C with 0.1 x SSC. The Southern blot did confirm the PCR fragments as hRUP4.

c. hRUP5

RT-PCR was performed using the following hRUP5 specific primers:

5'-CTGACTTCTTGTTCTGTCAGCAGCGG-3' (SEQ.ID.NO.: 63; sense)

5'-AGACCAGCCAGGGCACGCTGAAGAGTG-3' (SEQ.ID.NO.: 64; antisense)

and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) was used for the amplification in a 40ul reaction by the following cycles: 94°C for 30 sec, 94°C for 10 sec, 62°C for 1.5 min, 72°C for 5 min, and with cycles 2 through 3 repeated 30 times. 20 µl of the reaction were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and hRUP5 mRNA was found expressed only in the peripheral blood leukocytes (*data not shown*).

10 d. hRUP6

RT-PCR was applied to confirm the expression and to determine the tissue distribution of hRUP6. Oligonucleotides used, based on an alignment of AC005871 and GPR66 segments, had the following sequences:

5'-CCAACACCAGCATCCATGGCATCAAG-3' (SEQ.ID.NO.: 73; sense),

15 5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 74; antisense)

and the human multiple tissue cDNA panels (MTC, Clontech) were used as templates.

PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions will be followed) in a 40ul reaction by the following cycles: 94°C for 30 sec; 94°C 5 sec; 66°C for 40 sec, 72°C for 2.5 min, and 72°C for 7 min. Cycles 2 through 4
20 were repeated 30 times.

20 ul of the reaction were loaded on a 1.2% agarose gel to analyze the RT-PCR products, and a specific 760bp DNA fragment representing hRUP6 was expressed predominantly in the thymus and with less expression in the heart, kidney, lung, prostate small intestine and testis. (*see, Figure 5*).

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention and the claims that follow.

Although a variety of Vectors are available to those in the art, for purposes of utilization for both endogenous and non-endogenous human GPCRs, it is most preferred that the Vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

CLAIMS

What is claimed is:

1. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 1.
- 5 2. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 1 comprising SEQ.ID.NO.: 2.
3. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:1.
4. A Host Cell comprising the Plasmid of claim 3.
5. A cDNA encoding a human G protein-coupled receptor comprising
10 SEQ.ID.NO.: 3.
6. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 3 comprising SEQ.ID.NO.: 4.
7. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:3.
8. A Host Cell comprising the Plasmid of claim 7.
- 15 9. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 5.
10. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 5 comprising SEQ.ID.NO.: 6.
11. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:5.
- 20 12. A Host Cell comprising the Plasmid of claim 11.
13. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 7.

- 32 -

14. A human G protein-coupled receptor encoded by the cDNA of SEQ.ID.NO.: 7 comprising SEQ.ID.NO.: 8.
15. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:7.
16. A Host Cell comprising the Plasmid of claim 15.
- 5 17. A cDNA encoding a human G protein-coupled receptor comprising SEQ.ID.NO.: 9.
18. A human G protein-coupled receptor encoded by the cDNA of SEQ.ID.NO.: 9 comprising SEQ.ID.NO.: 10.
19. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:9.
- 10 20. A Host Cell comprising the Plasmid of claim 19.
21. A cDNA encoding a human G protein-coupled receptor comprising SEQ.ID.NO.: 11.
22. A human G protein-coupled receptor encoded by the cDNA of SEQ.ID.NO.: 11 comprising SEQ.ID.NO.:12.
- 15 23. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:11.
24. A Host Cell comprising the Plasmid of claim 23.
25. A cDNA encoding a human G protein-coupled receptor comprising SEQ.ID.NO.: 13.
26. A human G protein-coupled receptor encoded by the cDNA of 20 SEQ.ID.NO.: 13 comprising SEQ.ID.NO.: 14.
27. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:13.
28. A Host Cell comprising the Plasmid of claim 27.
29. A cDNA encoding a human G protein-coupled receptor comprising

- 33 -

SEQ.ID.NO.: 15.

30. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 15 comprising SEQ.ID.NO.: 16.

31. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:15.

5 32. A Host Cell comprising the Plasmid of claim 31.

33. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 17.

34. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 17 comprising SEQ.ID.NO.: 18.

10 35. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:17.

36. A Host Cell comprising the Plasmid of claim 35.

37. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 19.

38. A human G protein-coupled receptor encoded by the cDNA of
15 SEQ.ID.NO.: 19 comprising SEQ.ID.NO.: 20.

39. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:19.

40. A Host Cell comprising the Plasmid of claim 39.

41. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 21.

20 42. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 21 comprising SEQ.ID.NO.: 22.

43. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:21.

44. A Host Cell comprising the Plasmid of claim 43.

- 34 -

45. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 23.
46. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 23 comprising SEQ.ID.NO.: 24.
- 5 47. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.: 23.
48. A Host Cell comprising the Plasmid of claim 47.
49. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 25.
50. A human G protein-coupled receptor encoded by the cDNA of
10 SEQ.ID.NO.: 25 comprising SEQ.ID.NO.: 26.
51. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:25.
52. A Host Cell comprising the Plasmid of claim 51.
53. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 27.
- 15 54. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 27 comprising SEQ.ID.NO.: 28.
55. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:27.
56. A Host Cell comprising the Plasmid of claim 55.
57. A cDNA encoding a human G protein-coupled receptor comprising
20 SEQ.ID.NO.: 29.
58. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 29 comprising SEQ.ID.NO.: 30.
59. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:29.

- 35 -

60. A Host Cell comprising the Plasmid of claim 59.
61. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 31.
62. A human G protein-coupled receptor encoded by the cDNA of
5 SEQ.ID.NO.: 31 comprising SEQ.ID.NO.: 32.
63. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:31.
64. A Host Cell comprising the Plasmid of claim 63.
65. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 33.
- 10 66. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 33 comprising SEQ.ID.NO.: 34.
67. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:33.
68. A Host Cell comprising the Plasmid of claim 67.
69. A cDNA encoding a human G protein-coupled receptor comprising
15 SEQ.ID.NO.: 35.
70. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 35 comprising SEQ.ID.NO.: 36.
71. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:35.
72. A Host Cell comprising the Plasmid of claim 71.
- 20 73. A cDNA encoding a human G protein-coupled receptor comprising
SEQ.ID.NO.: 37.
74. A human G protein-coupled receptor encoded by the cDNA of
SEQ.ID.NO.: 37 comprising SEQ.ID.NO.: 38.

- 36 -

75. A Plasmid comprising a Vector and the cDNA of SEQ.ID.NO.:37.
76. A Host Cell comprising the Plasmid of claim 75.

1/4

	1	2	3	4	5	6	7	8
A		Amygdala	Caudate Nucleus	Cerebellum	Cerebral Cortex	Frontal Cortex	Hippocampus	Medulla Oblongata
B	Occipital Cortex	Putamen	Substantia Nigra	Temporal Cortex	Thalamus	Accumbens	Spinal Cord	
C	Heart	Aorta	Skeletal Muscle	Colon	Bladder	Uterus	Prostate	Stomach
D	Testis	Ovary	Pancreas	Pituitary	Adrenal Gland	Thyroid	Salivary Gland	Mammary Gland
E	Kidney	Liver	Small Intestine	Spleen	Thymus	Peripheral Leukocyte	Lymph Node	Bone Marrow
F	Appendix	Lung	Trachea	Placenta				
G	Fetal Brain	Fetal Heart	Fetal Kidney	Fetal Liver	Fetal Spleen	Fetal Thymus	Fetal Lung	
H								

FIG. 1A

	1	2	3	4	5	6	7	8	9	10	11	12
A		Cerebellum Left	Substantia Nigra	Heart	Esophagus	Colon Transverse	Kidney	Lung	Liver	Leukemia HL-60	Fetal Brain	
B	Cerebral Cortex	Cerebellum Right	Accumbens	Aorta	Stomach	Colon Descending	Skeletal Muscle	Placenta	Pancreas	HeLa S3	Fetal Heart	
C	Frontal Cortex	Corpus Callosum	Thalamus	Atrium Left	Duodenum	Rectum	Spleen	Bladder	Adrenal Gland	Leukemia K562	Fetal Kidney	
D	Parietal Lobe	Amygdala	Pituitary Gland	Atrium Right	Jejunum		Thymus	Uterus	Thyroid	Leukemia MOLT-4	Fetal Liver	
E	Occipital Cortex	Caudate Nucleus	Spinal Cord	Ventricle Left	Ileum		Peripheral Leukocyte	Prostate	Salivary Gland	Burkitt's Lymphoma	Fetal Spleen	
F	Temporal Cortex	Hippocampus		Ventricle Right	Ileocecum		Lymph Node	Testis	Mammary Gland	Burkitt's Lymphoma	Fetal Thymus	
G	Paracentral Gyrus of Cerebral Cortex	Medulla Oblongata		Inter Ventricular Septum	Appendix		Bone Marrow	Ovary		Daudi	Fetal Lung	
H	Pons	Putamen		Apex of the Heart	Colon Ascending		Trachea			Colorectal Adenocarcinoma SW480		
										Lung Carcinoma A549		

FIG. 1B

3/4

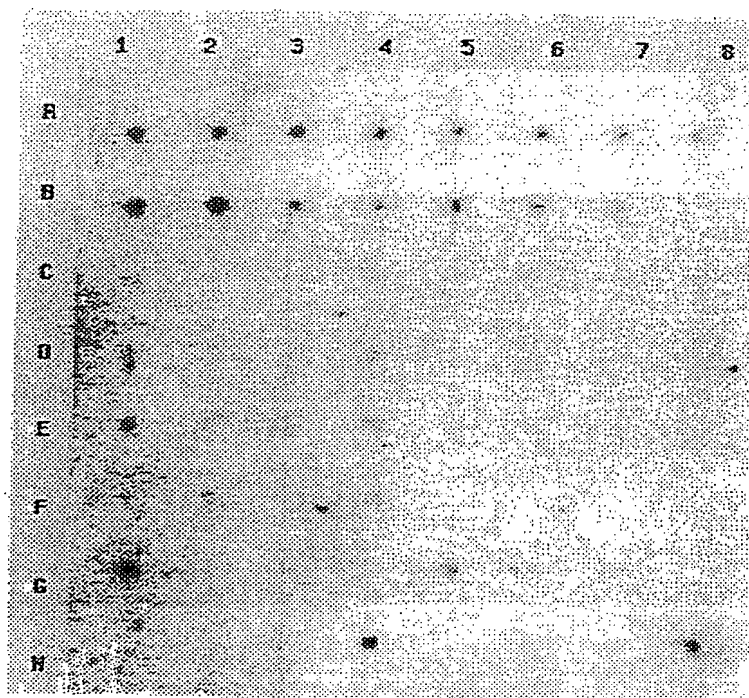
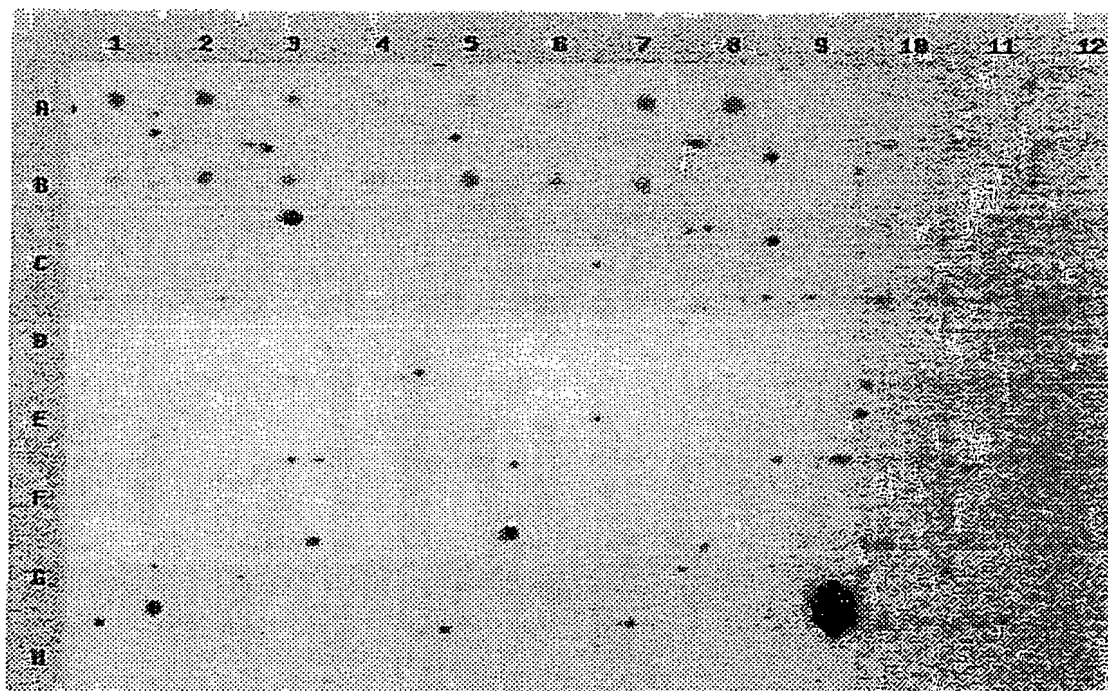
*FIG. 2A**FIG. 2B*

FIG. 5

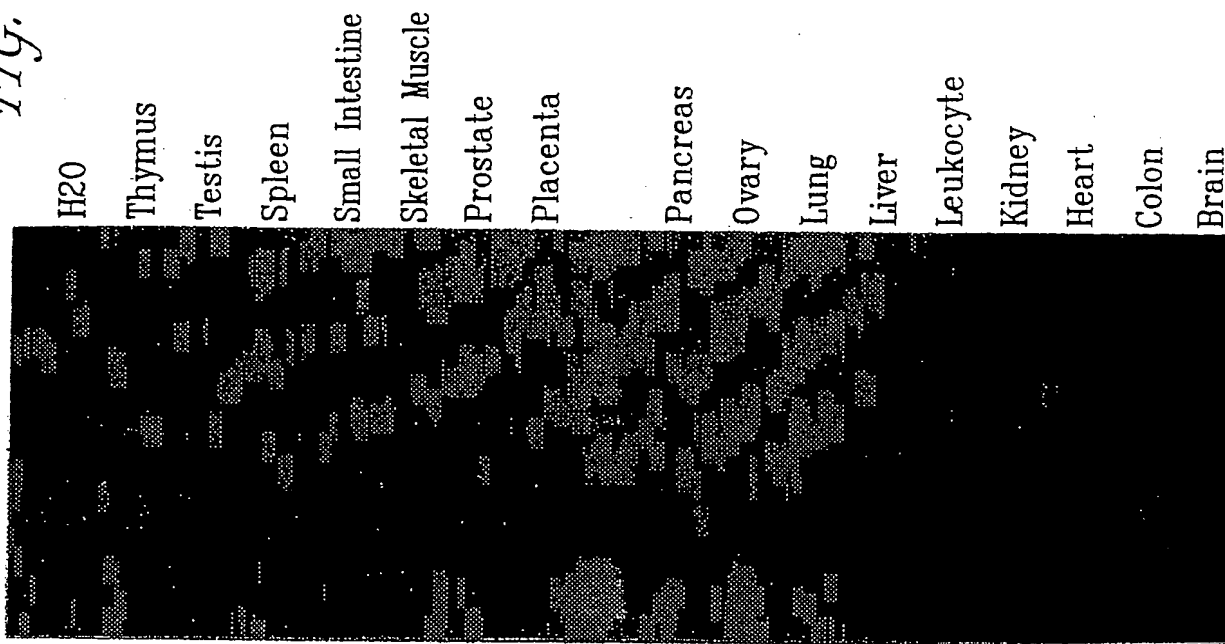


FIG. 4

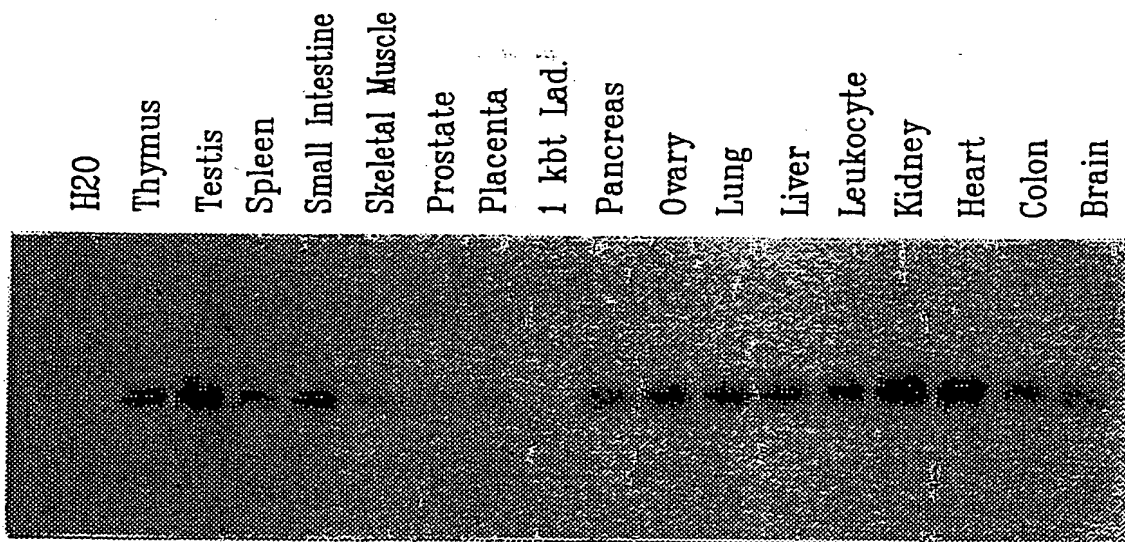
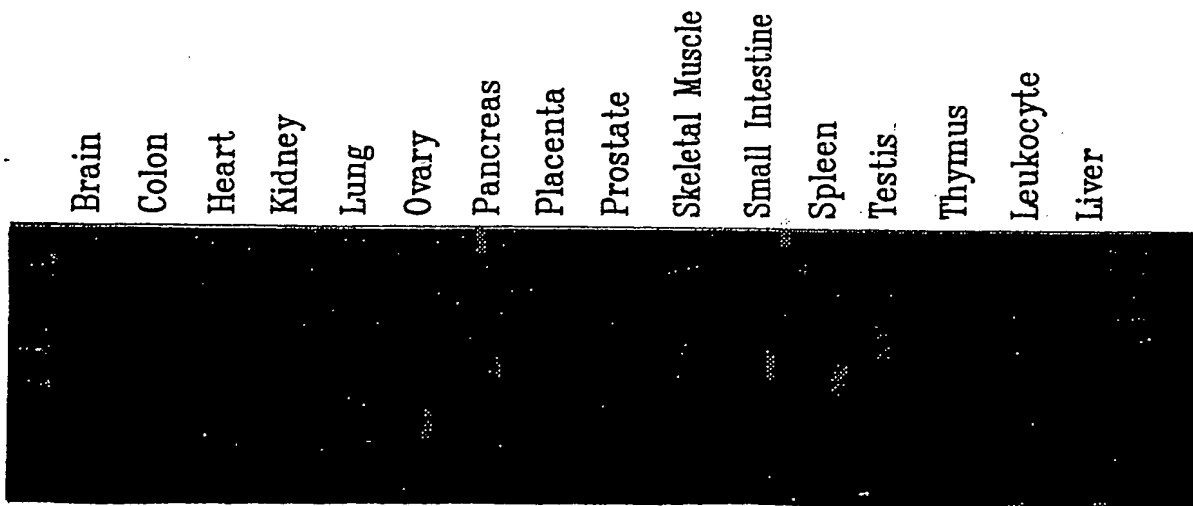


FIG. 3



- 1 -

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Chen, Ruoping
Dang, Huong T.
5 Liaw, Chen W.
Lin, I-Lin
- (ii) TITLE OF INVENTION: Human Orphan G Protein-Coupled Receptors
- (iii) NUMBER OF SEQUENCES: 74
- 10 (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Arena Pharmaceuticals, Inc.
(B) STREET: 6166 Nancy Ridge Drive
(C) CITY: San Diego
(D) STATE: CA
15 (E) COUNTRY: USA
(F) ZIP: 92121
- (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
20 (C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US
(B) FILING DATE:
25 (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Burgoon, Richard P.
(B) REGISTRATION NUMBER: 34,787
- (ix) TELECOMMUNICATION INFORMATION:
30 (A) TELEPHONE: (858)453-7200
(B) TELEFAX: (858)453-7210

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
35 (A) LENGTH: 1260 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

40 ATGGTCTTCT CGGCAGTGTT GACTGCGTTC CATACCGGGA CATCCAACAC AACATTTGTC 60

- 2 -

GTGTATGAAA ACACCTACAT GAATATTACA CTCCCTCCAC CATTCCAGCA TCCTGACCTC 120
AGTCCATTGC TTAGATATAG TTTTGAAACC ATGGCTCCCA CTGGTTTGAG TTCCTTGACC 180
GTGAATAGTA CAGCTGTGCC CACAACACCA GCAGCATTTA AGAGCCTAAA CTTGCCTCTT 240
CAGATCACCC TTTCTGCTAT AATGATATTC ATTCTGTTTG TGTCTTTTCT TGGGAACCTG 300
5 GTTGTTTGCC TCATGGTTTA CCAAAAAGCT GCCATGAGGT CTGCAATTAA CATCCTCCTT 360
GCCAGCCTAG CTTTTGCAGA CATGTTGCTT GCAGTGCTGA ACATGCCCTT TGCCCTGGTA 420
ACTATTCTTA CTACCCGATG GATTTTTTGGG AAATTCTTCT GTAGGGTATC TGCTATGTTT 480
TTCTGGTTAT TTGTGATAGA AGGAGTAGCC ATCCTGCTCA TCATTAGCAT AGATAGGTTT 540
CTTATTATAG TCCAGAGGCA GGATAAGCTA AATCCATATA GAGCTAAGGT TCTGATTGCA 600
10 GTTTCTTGGG CAACTTCCTT TTGTGTAGCT TTTCTTTAG CCGTAGGAAA CCCCACCTG 660
CAGATACCTT CCCGAGCTCC CCAGTGTGTG TTTGGGTACA CAACCAATCC AGGCTACCAG 720
GCTTATGTGA TTTTGATTTC TCTCATTTCT TTCTTCATAC CCTTCCTGGT AATACTGTAC 780
TCATTTATGG GCATACTCAA CACCCTTCGG CACAATGCCT TGAGGATCCA TAGCTACCCT 840
GAAGGTATAT GCCTCAGCCA GGCCAGCAA CTGGGTCTCA TGAGTCTGCA GAGACCTTTC 900
15 CAGATGAGCA TTGACATGGG CTTTAAACA CGTGCCTTCA CCACTATTTT GATTCTCTTT 960
GCTGTCTTCA TTGTCTGCTG GGCCCCATTC ACCACTTACA GCCTTGTGGC
AACATTCAGT1020
AAGCACTTTT ACTATCAGCA CAACTTTTTT GAGATTAGCA CCTGGCTACT GTGGCTCTGC1080
TACCTCAAGT CTGCATTGAA TCCGCTGATC TACTACTGGA GGATTAAGAA ATTCCATGAT1140
20 GCTTGCCTGG ACATGATGCC TAAGTCCTTC AAGTTTTTGC CGCAGCTCCC TGGTCACACA1200
AAGCGACGGA TACGTCCTAG TGCTGTCTAT GTGTGTGGGG AACATCGGAC GGTGGTGTGA1260

(3) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 419 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

30 Met Val Phe Ser Ala Val Leu Thr Ala Phe His Thr Gly Thr Ser Asn
1 5 10 15

- 3 -

Thr Thr Phe Val Val Tyr Glu Asn Thr Tyr Met Asn Ile Thr Leu Pro
 20 25 30
 Pro Pro Phe Gln His Pro Asp Leu Ser Pro Leu Leu Arg Tyr Ser Phe
 35 40 45
 5 Glu Thr Met Ala Pro Thr Gly Leu Ser Ser Leu Thr Val Asn Ser Thr
 50 55 60
 Ala Val Pro Thr Thr Pro Ala Ala Phe Lys Ser Leu Asn Leu Pro Leu
 65 70 75 80
 10 Gln Ile Thr Leu Ser Ala Ile Met Ile Phe Ile Leu Phe Val Ser Phe
 85 90 95
 Leu Gly Asn Leu Val Val Cys Leu Met Val Tyr Gln Lys Ala Ala Met
 100 105 110
 Arg Ser Ala Ile Asn Ile Leu Leu Ala Ser Leu Ala Phe Ala Asp Met
 115 120 125
 15 Leu Leu Ala Val Leu Asn Met Pro Phe Ala Leu Val Thr Ile Leu Thr
 130 135 140
 Thr Arg Trp Ile Phe Gly Lys Phe Phe Cys Arg Val Ser Ala Met Phe
 145 150 155 160
 20 Phe Trp Leu Phe Val Ile Glu Gly Val Ala Ile Leu Leu Ile Ile Ser
 165 170 175
 Ile Asp Arg Phe Leu Ile Ile Val Gln Arg Gln Asp Lys Leu Asn Pro
 180 185 190
 Tyr Arg Ala Lys Val Leu Ile Ala Val Ser Trp Ala Thr Ser Phe Cys
 195 200 205
 25 Val Ala Phe Pro Leu Ala Val Gly Asn Pro Asp Leu Gln Ile Pro Ser
 210 215 220
 Arg Ala Pro Gln Cys Val Phe Gly Tyr Thr Thr Asn Pro Gly Tyr Gln
 225 230 235 240
 30 Ala Tyr Val Ile Leu Ile Ser Leu Ile Ser Phe Phe Ile Pro Phe Leu
 245 250 255
 Val Ile Leu Tyr Ser Phe Met Gly Ile Leu Asn Thr Leu Arg His Asn
 260 265 270
 Ala Leu Arg Ile His Ser Tyr Pro Glu Gly Ile Cys Leu Ser Gln Ala
 275 280 285
 35 Ser Lys Leu Gly Leu Met Ser Leu Gln Arg Pro Phe Gln Met Ser Ile
 290 295 300
 Asp Met Gly Phe Lys Thr Arg Ala Phe Thr Thr Ile Leu Ile Leu Phe

- 4 -

	305		310		315		320
	Ala Val Phe Ile Val Cys Trp Ala Pro Phe Thr Thr Tyr Ser Leu Val						
		325			330		335
5	Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe Glu Ile						
		340			345		350
	Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala Leu Asn Pro						
		355			360		365
	Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp Ala Cys Leu Asp						
		370			375		380
10	Met Met Pro Lys Ser Phe Lys Phe Leu Pro Gln Leu Pro Gly His Thr						
		385			390		395
	Lys Arg Arg Ile Arg Pro Ser Ala Val Tyr Val Cys Gly Glu His Arg						
		405			410		415
	Thr Val Val						
15							

(4) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1119 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATGTTAGCCA ACAGCTCCTC AACCAACAGT TCTGTTCTCC CGTGTCTGA CTACCGACCT 60
 25 ACCCAACCGCC TGCACTTGGT GGTCTACAGC TTGGTGCTGG CTGCCGGGCT CCCCTCAAC 120
 GCGCTAGCCC TCTGGGTCTT CCTGCGCGCG CTGCGCGTGC ACTCGGTGGT GAGCGTGTAC 180
 ATGTGTAACC TGGCGGCCAG CGACCTGCTC TTCACCTCT CGCTGCCCCG TCGTCTCTCC 240
 TACTACGCAC TGCACCACTG GCCCTTCCCC GACCTCCTGT GCCAGACGAC GGGCGCCATC 300
 TTCCAGATGA ACATGTACGG CAGCTGCATC TTCCTGATGC TCATCAACGT GGACCGCTAC 360
 30 GCCGCCATCG TGCACCCGCT GCGACTGCGC CACCTGCGGC GGCCCCGCGT GCGCGGCTG 420
 CTCTGCCTGG GCGTGTGGGC GCTCATCCTG GTGTTTGCCG TGCCCGCCGC CCGCGTGCAC 480
 AGGCCCTCGC GTTGCCGCTA CCGGGACCTC GAGGTGCGCC TATGCTTCGA GAGCTTCAGC 540
 GACGAGCTGT GGAAAGGCAG GCTGCTGCCC CTCGTGCTGC TGGCCGAGGC GCTGGGCTTC 600

- 5 -

CTGCTGCCCC TGGCGGCGGT GGTCTACTCG TCGGGCCGAG TCTTCTGGAC GCTGGCGCGC 660
 CCCGACGCCA CGCAGAGCCA GCGGCGGCGG AAGACCGTGC GCCTCCTGCT GGCTAACCTC 720
 GTCATCTTCC TGCTGTGCTT CGTGCCCTAC AACAGCACGC TGGCGGTCTA CGGGCTGCTG 780
 CGGAGCAAGC TGGTGGCGGC CAGCGTGCCT GCCCGCGATC GCGTGC GCGG GGTGCTGATG 840
 5 GTGATGGTGC TGCTGGCCGG CGCCAACTGC GTGCTGGACC CGCTGGTGTA CTACTTTAGC 900
 GCCGAGGGCT TCCGCAACAC CCTGCGCGGC CTGGGCACTC CGCACC GGGC CAGGACCTCG 960
 GCCACCAACG GGACGCGGGC GCGCTCGCG CAATCCGAAA GGTCCGCCGT CACCACCGAC1020
 GCCACCAGGC CGGATGCCGC CAGTCAGGGG CTGCTCCGAC CCTCCGACTC CCACTCTCTG1080
 TCTTCCTTCA CACAGTGTCC CCAGGATTCC GCCCTCTGA 1119

10 (5) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 372 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 15 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Leu Ala Asn Ser Ser Ser Thr Asn Ser Ser Val Leu Pro Cys Pro
 1 5 10 15
 20 Asp Tyr Arg Pro Thr His Arg Leu His Leu Val Val Tyr Ser Leu Val
 20 25 30
 Leu Ala Ala Gly Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu
 35 40 45
 25 Arg Ala Leu Arg Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu
 50 55 60
 Ala Ala Ser Asp Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser
 65 70 75 80
 Tyr Tyr Ala Leu His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr
 85 90 95
 30 Thr Gly Ala Ile Phe Gln Met Asn Met Tyr Gly Ser Cys Ile Phe Leu
 100 105 110
 Met Leu Ile Asn Val Asp Arg Tyr Ala Ala Ile Val His Pro Leu Arg
 115 120 125

- 6 -

Leu Arg His Leu Arg Arg Pro Arg Val Ala Arg Leu Leu Cys Leu Gly
 130 135 140
 Val Trp Ala Leu Ile Leu Val Phe Ala Val Pro Ala Ala Arg Val His
 145 150 155 160
 5 Arg Pro Ser Arg Cys Arg Tyr Arg Asp Leu Glu Val Arg Leu Cys Phe
 165 170 175
 Glu Ser Phe Ser Asp Glu Leu Trp Lys Gly Arg Leu Leu Pro Leu Val
 180 185 190
 10 Leu Leu Ala Glu Ala Leu Gly Phe Leu Leu Pro Leu Ala Ala Val Val
 195 200 205
 Tyr Ser Ser Gly Arg Val Phe Trp Thr Leu Ala Arg Pro Asp Ala Thr
 210 215 220
 Gln Ser Gln Arg Arg Arg Lys Thr Val Arg Leu Leu Leu Ala Asn Leu
 225 230 235 240
 15 Val Ile Phe Leu Leu Cys Phe Val Pro Tyr Asn Ser Thr Leu Ala Val
 245 250 255
 Tyr Gly Leu Leu Arg Ser Lys Leu Val Ala Ala Ser Val Pro Ala Arg
 260 265 270
 20 Asp Arg Val Arg Gly Val Leu Met Val Met Val Leu Leu Ala Gly Ala
 275 280 285
 Asn Cys Val Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ala Glu Gly Phe
 290 295 300
 Arg Asn Thr Leu Arg Gly Leu Gly Thr Pro His Arg Ala Arg Thr Ser
 305 310 315 320
 25 Ala Thr Asn Gly Thr Arg Ala Ala Leu Ala Gln Ser Glu Arg Ser Ala
 325 330 335
 Val Thr Thr Asp Ala Thr Arg Pro Asp Ala Ala Ser Gln Gly Leu Leu
 340 345 350
 30 Arg Pro Ser Asp Ser His Ser Leu Ser Ser Phe Thr Gln Cys Pro Gln
 355 360 365
 Asp Ser Ala Leu
 370

(6) INFORMATION FOR SEQ ID NO.:5:

(1) SEQUENCE CHARACTERISTICS:

- 35 (A) LENGTH: 1107 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- 7 -

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ATGGCCAACT CCACAGGGCT GAACGCCTCA GAAGTCGCAG GCTCGTTGGG GTTGATCCTG 60
 GCAGCTGTCTG TGGAGGTGGG GGCAGTGTCTG GGCAACGGCG CGCTGCTGGT CGTGGTGTCTG 120
 5 CGCACGCCGG GACTGCGCGA CGCGCTCTAC CTGGCGCACC TGTGCGTCGT GGACCTGTCTG 180
 GCGGCCGCCT CCATCATGCC GCTGGGCCTG CTGGCCGCAC CGCCGCCCGG GCTGGGGCCGC 240
 GTGCGCCTGG GCCCCGCGCC ATGCCGCGCC GCTCGCTTCC TCTCCGCCGC TCTGCTGCCG 300
 GCCTGCACGC TCGGGGTGGC CGCACTTGGC CTGGCAGCT ACCGCCTCAT CGTGCACCCG 360
 CTGCGGCCAG GCTCGCGGCC GCCGCCTGTG CTCGTGCTCA CCGCCGTGTG GGCCGCGGCG 420
 10 GGAAGTGTCTG GCGCGCTCTC CCGCTCGGC CCGCCGCCCG CACCGCCCCC TGCTCCTGCT 480
 CGCTGCTCGG TCCTGGCTGG GGGCCTCGGG CCCTTCCGGC CGCTCTGGGC CCTGCTGGCC 540
 TTCGCGCTGC CCGCCCTCCT GCTGCTCGGC GCCTACGGCG GCATCTTCGT GGTGGCGCGT 600
 CGCGCTGCCC TGAGGCCCCC ACGGCCGCG CGCGGGTCCC GACTCCGCTC GGACTCTCTG 660
 GATAGCCGCC TTTCCATCTT GCCGCCGCTC CGGCCTCGCC TGCCCGGGGG CAAGGCGGCC 720
 15 CTGGCCCCAG CGCTGGCCGT GGGCCAATTT GCAGCCTGCT GGCTGCCTTA TGGCTGCGCG 780
 TGCCTGGCGC CCGCAGCGCG GGCCGCGGAA GCCGAAGCGG CTGTCACCTG GGTGCGCTAC 840
 TCGGCCTTCG CGGCTCAGCC CTTCTGTAC GGGCTGCTGC AGCGCCCCGT GCGCTTGGCA 900
 CTGGGCCGCC TCTCTCGCCG TGCACTGCCT GGACCTGTGC GGGCCTGCAC TCCGCAAGCC 960
 TGGCACCCGC GGGCACTCTT GCAATGCCTC CAGAGACCCC CAGAGGGCCC TGCCGTAGGC 1020
 20 CCTTCTGAGG CTCCAGAACA GACCCCCGAG TTGGCAGGAG GGCGGAGCCC CGCATAACAG 1080
 GGGCCACCTG AGAGTTCTCT CTCCTGA 1107

(7) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 368 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

- 8 -

Met Ala Asn Ser Thr Gly Leu Asn Ala Ser Glu Val Ala Gly Ser Leu
 1 5 10 15
 Gly Leu Ile Leu Ala Ala Val Val Glu Val Gly Ala Leu Leu Gly Asn
 20 25 30
 5 Gly Ala Leu Leu Val Val Val Leu Arg Thr Pro Gly Leu Arg Asp Ala
 35 40 45
 Leu Tyr Leu Ala His Leu Cys Val Val Asp Leu Leu Ala Ala Ala Ser
 50 55 60
 10 Ile Met Pro Leu Gly Leu Leu Ala Ala Pro Pro Pro Gly Leu Gly Arg
 65 70 75 80
 Val Arg Leu Gly Pro Ala Pro Cys Arg Ala Ala Arg Phe Leu Ser Ala
 85 90 95
 Ala Leu Leu Pro Ala Cys Thr Leu Gly Val Ala Ala Leu Gly Leu Ala
 100 105 110
 15 Arg Tyr Arg Leu Ile Val His Pro Leu Arg Pro Gly Ser Arg Pro Pro
 115 120 125
 Pro Val Leu Val Leu Thr Ala Val Trp Ala Ala Ala Gly Leu Leu Gly
 130 135 140
 20 Ala Leu Ser Leu Leu Gly Pro Pro Pro Ala Pro Pro Pro Ala Pro Ala
 145 150 155 160
 Arg Cys Ser Val Leu Ala Gly Gly Leu Gly Pro Phe Arg Pro Leu Trp
 165 170 175
 Ala Leu Leu Ala Phe Ala Leu Pro Ala Leu Leu Leu Leu Gly Ala Tyr
 180 185 190
 25 Gly Gly Ile Phe Val Val Ala Arg Arg Ala Ala Leu Arg Pro Pro Arg
 195 200 205
 Pro Ala Arg Gly Ser Arg Leu Arg Ser Asp Ser Leu Asp Ser Arg Leu
 210 215 220
 30 Ser Ile Leu Pro Pro Leu Arg Pro Arg Leu Pro Gly Gly Lys Ala Ala
 225 230 235 240
 Leu Ala Pro Ala Leu Ala Val Gly Gln Phe Ala Ala Cys Trp Leu Pro
 245 250 255
 Tyr Gly Cys Ala Cys Leu Ala Pro Ala Ala Arg Ala Ala Glu Ala Glu
 260 265 270
 35 Ala Ala Val Thr Trp Val Ala Tyr Ser Ala Phe Ala Ala His Pro Phe
 275 280 285
 Leu Tyr Gly Leu Leu Gln Arg Pro Val Arg Leu Ala Leu Gly Arg Leu

- 9 -

	290		295		300
	Ser Arg Arg Ala Leu Pro Gly Pro Val Arg Ala Cys Thr Pro Gln Ala				
	305		310		315 320
5	Trp His Pro Arg Ala Leu Leu Gln Cys Leu Gln Arg Pro Pro Glu Gly				
		325		330	335
	Pro Ala Val Gly Pro Ser Glu Ala Pro Glu Gln Thr Pro Glu Leu Ala				
		340		345	350
	Gly Gly Arg Ser Pro Ala Tyr Gln Gly Pro Pro Glu Ser Ser Leu Ser				
		355		360	365

10 (8) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1008 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATGGAATCAT CTTTCTCATT TGGAGTGATC CTTGCTGTCC TGGCCTCCCT CATCATTGCT 60
 ACTAACACAC TAGTGGCTGT GGCTGTGCTG CTGTTGATCC ACAAGAATGA TGGTGTCACT 120
 20 CTCTGCTTCA CCTTGAATCT GGCTGTGGCT GACACCTTGA TTGGTGTGGC CATCTCTGGC 180
 CTACTCACAG ACCAGCTCTC CAGCCCTTCT CGGCCACAC AGAAGACCCT GTGCAGCCTG 240
 CGGATGGCAT TTGTCACTTC CTCCGAGCT GCCTCTGTCC TCACGGTCAT GCTGATCACC 300
 TTTGACAGGT ACCTTGCCAT CAAGCAGCCC TTCCGCTACT TGAAGATCAT GAGTGGGTTC 360
 GTGGCCGGGG CCTGCATTGC CGGGCTGTGG TTAGTGTCTT ACCTCATTGG CTTCTCTCCA 420
 25 CTCGGAATCC CCATGTTCCA GCAGACTGCC TACAAAGGGC AGTGCAGCTT CTTTGCTGTA 480
 TTTCAACCTC ACTTCGTGCT GACCCTCTCC TGCCTTGGCT TCTTCCCAGC CATGCTCCTC 540
 TTTGTCTTCT TCTACTGCGA CATGCTCAAG ATTGCCTCCA TGCACAGCCA GCAGATTCTGA 600
 AAGATGGAAC ATGCAGGAGC CATGGCTGGA GGTATCGAT CCCCACGGAC TCCCAGCGAC 660
 TTCAAAGCTC TCCGTACTGT GTCTGTTCTC ATTGGGAGCT TTGCTCTATC CTGGACCCCC 720
 30 TTCCTTATCA CTGGCATTGT GCAGGTGGCC TGCCAGGAGT GTCACCTCTA CCTAGTGCTG 780
 GAACGGTACC TGTGGCTGCT CGGCGTGGGC AACTCCCTGC TCAACCCACT CATCTATGCC 840

- 10 -

TATTGGCAGA AGGAGGTGCG ACTGCAGCTC TACCACATGG CCCTAGGAGT GAAGAAGGTG 900
 CTCACCTCAT TCCTCCTCTT TCTCTCGGCC AGGAATTGTG GCCCAGAGAG GCCCAGGGAA 960
 AGTTCCTGTC ACATCGTCAC TATCTCCAGC TCAGAGTTTG ATGGCTAA 1008

(9) INFORMATION FOR SEQ ID NO:8:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 335 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

- 10 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala Ser
 1 5 10 15
 Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu
 15 20 25 30
 Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala
 35 40 45
 Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp
 50 55 60
 Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu
 65 70 75 80
 Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val
 85 90 95
 Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg
 25 100 105 110
 Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly
 115 120 125
 Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro
 130 135 140
 Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val
 30 145 150 155 160
 Phe His Pro His Phe Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro
 165 170 175
 Ala Met Leu Leu Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala
 35 180 185 190

- 11 -

Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met
 195 200 205

Ala Gly Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu
 210 215 220

5 Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro
 225 230 235 240

Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His Leu
 245 250 255

10 Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly Asn Ser
 260 265 270

Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu Val Arg Leu
 275 280 285

Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val Leu Thr Ser Phe
 290 295 300

15 Leu Leu Phe Leu Ser Ala Arg Asn Cys Gly Pro Glu Arg Pro Arg Glu
 305 310 315 320

Ser Ser Cys His Ile Val Thr Ile Ser Ser Ser Glu Phe Asp Gly
 325 330 335

(10) INFORMATION FOR SEQ ID NO:9:

- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1413 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- 25 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ATGGACACTA CCATGGAAGC TGACCTGGGT GCCACTGGCC ACAGGCCCCG CACAGAGCTT 60
 GATGATGAGG ACTCCTACCC CCAAGGTGGC TGGGACACGG TCTTCCTGGT GGCCCTGCTG 120
 CTCCTTGGGC TGCCAGCCAA TGGGTTGATG GCGTGGCTGG CCGGCTCCCA GGCCCGGCAT 180
 30 GGAGCTGGCA CGCGTCTGGC GCTGCTCCTG CTCAGCCTGG CCCTCTCTGA CTTCTTGTTT 240
 CTGGCAGCAG CGGCCTTCCA GATCCTAGAG ATCCGGCATG GGGGACACTG GCCGCTGGGG 300
 ACAGCTGCCT GCCGCTTCTA CTACTTCCTA TGGGGCGTGT CCTACTCCTC CGGCCTCTTC 360
 CTGCTGGCCG CCCTCAGCCT CGACCGCTGC CTGCTGGCGC TGTGCCCACA CTGGTACCCT 420
 GGGCACCGCC CAGTCCGCCT GCCCCTCTGG GTCTGCGCCG GTGTCTGGGT GCTGGCCACA 480

- 12 -

CTCTTCAGCG TGCCCTGGCT GGTCTTCCCC GAGGCTGCCG TCTGGTGGTA CGACCTGGTC 540
 ATCTGCCTGG ACTTCTGGGA CAGCGAGGAG CTGTCGCTGA GGATGCTGGA GGTCTGGGG 600
 GGCTTCCTGC CTTTCCTCCT GCTGCTCGTC TGCCACGTGC TCACCCAGGC CACAGCCTGT 660
 CGCACCTGCC ACCGCCAACA GCAGCCCGCA GCCTGCCGGG GCTTCGCCCC TGTGGCCAGG 720
 5 ACCATTCTGT CAGCCTATGT GGTCTGAGG CTGCCCTACC AGCTGGCCCA GCTGCTCTAC 780
 CTGGCCTTCC TGTGGGACGT CTACTCTGGC TACCTGCTCT GGGAGGCCCT GGTCTACTCC 840
 GACTACCTGA TCCTACTCAA CAGCTGCCTC AGCCCCCTTCC TCTGCCTCAT GGCCAGTGCC 900
 GACCTCCGGA CCCTGCTGCG CTCGCTGCTC TCGTCCTTCG CGGCAGCTCT CTGCGAGGAG 960
 CGGCCGGGCA GCTTCACGCC CACTGAGCCA CAGACCCAGC TAGATTCTGA GGTCCAAC1020
 10 CTGCCAGAGC CGATGGCAGA GGCCCACTCA CAGATGGATC CTGTGGCCCA GCCTCAGGTG1080
 AACCCACAC TCCAGCCACG ATCGGATCCC ACAGCTCAGC CACAGCTGAA CCCTACGGCC1140
 CAGCCACAGT CGGATCCAC AGCCAGCCA CAGCTGAACC TCATGGCCCA GCCACAGTCA1200
 GATTCTGTGG CCCAGCCACA GGCAGACACT AACGTCCAGA CCCCTGCACC TGCTGCCAGT1260
 TCTGTGCCCA GTCCCTGTGA TGAAGCTTCC CCAACCCCAT CCTCGCATCC TACCCAGGG1320
 15 GCCCTTGAGG ACCCAGCCAC ACCTCCTGCC TCTGAAGGAG AAAGCCCCAG CAGCACCCCG1380
 CCAGAGGCGG CCCCAGGCGC AGGCCCCACG TGA 1413

(11) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 468 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

25 Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg Pro
 1 5 10 15
 Arg Thr Glu Leu Asp Asp Glu Asp Ser Tyr Pro Gln Gly Gly Trp Asp
 20 25 30
 30 Thr Val Phe Leu Val Ala Leu Leu Leu Gly Leu Pro Ala Asn Gly
 35 40 45
 Leu Met Ala Trp Leu Ala Gly Ser Gln Ala Arg His Gly Ala Gly Thr

- 13 -

	50		55		60
	Arg Leu Ala Leu Leu Leu Leu Ser Leu Ala Leu Ser Asp Phe Leu Phe				
	65		70		75 80
5	Leu Ala Ala Ala Ala Phe Gln Ile Leu Glu Ile Arg His Gly Gly His				
		85		90	95
	Trp Pro Leu Gly Thr Ala Ala Cys Arg Phe Tyr Tyr Phe Leu Trp Gly				
		100		105	110
	Val Ser Tyr Ser Ser Gly Leu Phe Leu Leu Ala Ala Leu Ser Leu Asp				
		115		120	125
10	Arg Cys Leu Leu Ala Leu Cys Pro His Trp Tyr Pro Gly His Arg Pro				
		130		135	140
	Val Arg Leu Pro Leu Trp Val Cys Ala Gly Val Trp Val Leu Ala Thr				
		145		150	155 160
15	Leu Phe Ser Val Pro Trp Leu Val Phe Pro Glu Ala Ala Val Trp Trp				
		165		170	175
	Tyr Asp Leu Val Ile Cys Leu Asp Phe Trp Asp Ser Glu Glu Leu Ser				
		180		185	190
	Leu Arg Met Leu Glu Val Leu Gly Gly Phe Leu Pro Phe Leu Leu Leu				
		195		200	205
20	Leu Val Cys His Val Leu Thr Gln Ala Thr Arg Thr Cys His Arg Gln				
		210		215	220
	Gln Gln Pro Ala Ala Cys Arg Gly Phe Ala Arg Val Ala Arg Thr Ile				
		225		230	235 240
25	Leu Ser Ala Tyr Val Val Leu Arg Leu Pro Tyr Gln Leu Ala Gln Leu				
		245		250	255
	Leu Tyr Leu Ala Phe Leu Trp Asp Val Tyr Ser Gly Tyr Leu Leu Trp				
		260		265	270
	Glu Ala Leu Val Tyr Ser Asp Tyr Leu Ile Leu Leu Asn Ser Cys Leu				
		275		280	285
30	Ser Pro Phe Leu Cys Leu Met Ala Ser Ala Asp Leu Arg Thr Leu Leu				
		290		295	300
	Arg Ser Val Leu Ser Ser Phe Ala Ala Ala Leu Cys Glu Glu Arg Pro				
		305		310	315 320
35	Gly Ser Phe Thr Pro Thr Glu Pro Gln Thr Gln Leu Asp Ser Glu Gly				
		325		330	335
	Pro Thr Leu Pro Glu Pro Met Ala Glu Ala Gln Ser Gln Met Asp Pro				
		340		345	350

- 14 -

Val Ala Gln Pro Gln Val Asn Pro Thr Leu Gln Pro Arg Ser Asp Pro
355 360 365

Thr Ala Gln Pro Gln Leu Asn Pro Thr Ala Gln Pro Gln Ser Asp Pro
370 375 380

5 Thr Ala Gln Pro Gln Leu Asn Leu Met Ala Gln Pro Gln Ser Asp Ser
385 390 395 400

Val Ala Gln Pro Gln Ala Asp Thr Asn Val Gln Thr Pro Ala Pro Ala
405 410 415

10 Ala Ser Ser Val Pro Ser Pro Cys Asp Glu Ala Ser Pro Thr Pro Ser
420 425 430

Ser His Pro Thr Pro Gly Ala Leu Glu Asp Pro Ala Thr Pro Pro Ala
435 440 445

Ser Glu Gly Glu Ser Pro Ser Ser Thr Pro Pro Glu Ala Ala Pro Gly
450 455 460

15 Ala Gly Pro Thr
465

(12) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1248 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

25 ATGTCAGGGA TGA AAAA ACT TCAGAATGCT TCCTGGATCT ACCAGCAGAA ACTAGAAGAT 60
 CCATTCCAGA AACACCTGAA CAGCACCGAG GAGTATCTGG CCTTCCTCTG CGGACCTCGG 120
 CGCAGCCACT TCTTCCTCCC CGTGTCTGTG GTGTATGTGC CAATTTTTGT GGTGGGGGTC 180
 ATTGGCAATG TCCTGGTGTG CCTGGTGATT CTGCAGCACC AGGCTATGAA GACGCCACCC 240
 AACTACTACC TCTTCAGCCT GCGGTCTCT GACCTCCTGG TCCTGCTCCT TGGAAATGCCC 300
 30 CTGGAGGTCT ATGAGATGTG GCGCAACTAC CCTTTCTTGT TCGGGCCCGT GGGCTGCTAC 360
 TTCAAGACGG CCTCTTTGA GACCGTGTGC TTCGCCTCCA TCCTCAGCAT CACCACCGTC 420
 AGCGTGGAGC GCTACGTGGC CATCCTACAC CCGTTCCGCG CCAA ACTGCA GAGCACCCGG 480
 CGCCGGGCCC TCAGGATCCT CGGCATCGTC TGGGGCTTCT CCGTGCTCTT CTCCTGCCC 540

- 15 -

AACACCAGCA TCCATGGCAT CAAGTTCCAC TACTTCCCCA ATGGGTCCCT GGTCCCAGGT 600
 TCGGCCACCT GTACGGTCAT CAAGCCCATG TGGATCTACA ATTTTCATCAT CCAGGTCACC 660
 TCCTTCCTAT TCTACCTCCT CCCCATGACT GTCATCAGTG TCCTCTACTA CCTCATGGCA 720
 CTCAGACTAA AGAAAGACAA ATCTCTTGAG GCAGATGAAG GGAATGCAAA TATTCAAAGA 780
 5 CCCTGCAGAA AATCAGTCAA CAAGATGCTG TTTGTCTTGG TCTTAGTGTT TGCTATCTGT 840
 TGGGCCCCGT TCCACATTGA CCGACTCTTC TTCAGCTTTG TGGAGGAGTG GAGTGAATCC 900
 CTGGCTGCTG TGTTC AACCT CGTCCATGTG GTGTCAGGTG TCTTCTTCTA CCTGAGCTCA 960
 GCTGTCAACC CCATTATCTA TAACCTACTG TCTCGCCGCT TCCAGGCAGC ATTCCAGAAT1020
 GTGATCTCTT CTTTCCACAA ACAGTGGCAC TCCCAGCATG ACCCACAGTT GCCACCTGCC1080
 10 CAGCGGAACA TCTTCTGAC AGAATGCCAC TTTGTGGAGC TGACCGAAGA TATAGGTCCC1140
 CAATTCCCAT GTCAGTCATC CATGCACAAC TCTCACCTCC CAACAGCCCT CTCTAGTGAA1200
 CAGATGTCAA GAACAACTA TCAAAGCTTC CACTTTAACA AAACCTGA 1248

(13) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
 15 (A) LENGTH: 415 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Ser Gly Met Glu Lys Leu Gln Asn Ala Ser Trp Ile Tyr Gln Gln
 1 5 10 15
 Lys Leu Glu Asp Pro Phe Gln Lys His Leu Asn Ser Thr Glu Glu Tyr
 20 25 30
 25 Leu Ala Phe Leu Cys Gly Pro Arg Arg Ser His Phe Phe Leu Pro Val
 35 40 45
 Ser Val Val Tyr Val Pro Ile Phe Val Val Gly Val Ile Gly Asn Val
 50 55 60
 30 Leu Val Cys Leu Val Ile Leu Gln His Gln Ala Met Lys Thr Pro Thr
 65 70 75 80
 Asn Tyr Tyr Leu Phe Ser Leu Ala Val Ser Asp Leu Leu Val Leu Leu
 85 90 95

- 16 -

Leu Gly Met Pro Leu Glu Val Tyr Glu Met Trp Arg Asn Tyr Pro Phe
 100 105 110

Leu Phe Gly Pro Val Gly Cys Tyr Phe Lys Thr Ala Leu Phe Glu Thr
 115 120 125

5 Val Cys Phe Ala Ser Ile Leu Ser Ile Thr Thr Val Ser Val Glu Arg
 130 135 140

Tyr Val Ala Ile Leu His Pro Phe Arg Ala Lys Leu Gln Ser Thr Arg
 145 150 155 160

10 Arg Arg Ala Leu Arg Ile Leu Gly Ile Val Trp Gly Phe Ser Val Leu
 165 170 175

Phe Ser Leu Pro Asn Thr Ser Ile His Gly Ile Lys Phe His Tyr Phe
 180 185 190

Pro Asn Gly Ser Leu Val Pro Gly Ser Ala Thr Cys Thr Val Ile Lys
 195 200 205

15 Pro Met Trp Ile Tyr Asn Phe Ile Ile Gln Val Thr Ser Phe Leu Phe
 210 215 220

Tyr Leu Leu Pro Met Thr Val Ile Ser Val Leu Tyr Tyr Leu Met Ala
 225 230 235 240

20 Leu Arg Leu Lys Lys Asp Lys Ser Leu Glu Ala Asp Glu Gly Asn Ala
 245 250 255

Asn Ile Gln Arg Pro Cys Arg Lys Ser Val Asn Lys Met Leu Phe Val
 260 265 270

Leu Val Leu Val Phe Ala Ile Cys Trp Ala Pro Phe His Ile Asp Arg
 275 280 285

25 Leu Phe Phe Ser Phe Val Glu Glu Trp Ser Glu Ser Leu Ala Ala Val
 290 295 300

Phe Asn Leu Val His Val Val Ser Gly Val Phe Phe Tyr Leu Ser Ser
 305 310 315 320

30 Ala Val Asn Pro Ile Ile Tyr Asn Leu Leu Ser Arg Arg Phe Gln Ala
 325 330 335

Ala Phe Gln Asn Val Ile Ser Ser Phe His Lys Gln Trp His Ser Gln
 340 345 350

His Asp Pro Gln Leu Pro Pro Ala Gln Arg Asn Ile Phe Leu Thr Glu
 355 360 365

35 Cys His Phe Val Glu Leu Thr Glu Asp Ile Gly Pro Gln Phe Pro Cys
 370 375 380

Gln Ser Ser Met His Asn Ser His Leu Pro Thr Ala Leu Ser Ser Glu
 385 390 395 400

- 17 -

Gln Met Ser Arg Thr Asn Tyr Gln Ser Phe His Phe Asn Lys Thr
 405 410 415

(14) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1173 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATGCCAGATA CTAATAGCAC AATCAATTTA TCACTAAGCA CTCGTGTTAC TTTAGCATTT 60
 TTTATGTCCT TAGTAGCTTT TGCTATAATG CTAGGAAATG CTTTGATCAT TTTAGCTTTT 120
 GTGGTGGACA AAAACCTTAG ACATCGAAGT AGTTATTTTT TTCTTAACTT GGCCATCTCT 180
 GACTTCTTTG TGGGTGTGAT CTCCATTCCT TTGTACATCC CTCACACGCT GTTCGAATGG 240
 15 GATTTTGGAA AGGAAATCTG TGTATTTTGG CTCCTACTG ACTATCTGTT ATGTACAGCA 300
 TCTGTATATA ACATTGTCCT CATCAGCTAT GATCGATACC TGTCAGTCTC AAATGCTGTG 360
 TCTTATAGAA CTCAACATAC TGGGGTCTTG AAGATTGTTA CTCTGATGGT GGCCGTTTGG 420
 GTGCTGGCCT TCTTAGTGAA TGGGCCAATG ATTCTAGTTT CAGAGTCTTG GAAGGATGAA 480
 GGTAGTGAAT GTGAACCTGG ATTTTTTTTCG GAATGGTACA TCCTTGCCAT CACATCATTC 540
 20 TTGGAATTCG TGATCCCAGT CATCTTAGTC GCTTATTTCA ACATGAATAT TTATTGGAGC 600
 CTGTGGAAGC GTGATCATCT CAGTAGGTGC CAAAGCCATC CTGGACTGAC TGCTGTCTCT 660
 TCCAACATCT GTGGACACTC ATTCAGAGGT AGACTATCTT CAAGGAGATC TCTTTCTGCA 720
 TCGACAGAAG TTCCTGCATC CTTTCATTCA GAGAGACAGA GGAGAAAGAG TAGTCTCATG 780
 TTTTCCTCAA GAACCAAGAT GAATAGCAAT ACAATTGCTT CCAAATGGG TTCCTTCTCC 840
 25 CAATCAGATT CTGTAGCTCT TCACCAAAGG GAACATGTTG AACTGCTTAG AGCCAGGAGA 900
 TTAGCCAGT CACTGGCCAT TCTCTTAGGG GTTTTTGCTG TTTGCTGGSC TCCATATTCT 960
 CTGTTACAAA TTGTCCTTTC ATTTTATTCC TCAGCAACAG GTCCTAAATC AGTTTGGTAT 1020
 AGAATTGCAT TTTGGCTTCA GTGGTTCAAT TCCTTTGTCA ATCCTCTTTT GATCCATTG 1080
 TGTACACAAGC GCTTTCAAAA GGCTTTCTTG AAAATATTTT GTATAAAAAA GCAACCTCTA 1140
 30 CCATCACAAC ACAGTCGGTC AGTATCTTCT TAA 1173

- 18 -

(15) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 390 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

10 Met Pro Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val
 1 5 10 15
 Thr Leu Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly
 20 25 30
 Asn Ala Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His
 35 40 45
 15 Arg Ser Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val
 50 55 60
 Gly Val Ile Ser Ile Pro Leu Tyr Ile Pro His Thr Leu Phe Glu Trp
 65 70 75 80
 20 Asp Phe Gly Lys Glu Ile Cys Val Phe Trp Leu Thr Thr Asp Tyr Leu
 85 90 95
 Leu Cys Thr Ala Ser Val Tyr Asn Ile Val Leu Ile Ser Tyr Asp Arg
 100 105 110
 Tyr Leu Ser Val Ser Asn Ala Val Ser Tyr Arg Thr Gln His Thr Gly
 115 120 125
 25 Val Leu Lys Ile Val Thr Leu Met Val Ala Val Trp Val Leu Ala Phe
 130 135 140
 Leu Val Asn Gly Pro Met Ile Leu Val Ser Glu Ser Trp Lys Asp Glu
 145 150 155 160
 30 Gly Ser Glu Cys Glu Pro Gly Phe Phe Ser Glu Trp Tyr Ile Leu Ala
 165 170 175
 Ile Thr Ser Phe Leu Glu Phe Val Ile Pro Val Ile Leu Val Ala Tyr
 180 185 190
 Phe Asn Met Asn Ile Tyr Trp Ser Leu Trp Lys Arg Asp His Leu Ser
 195 200 205
 35 Arg Cys Gln Ser His Pro Gly Leu Thr Ala Val Ser Ser Asn Ile Cys
 210 215 220

- 19 -

Gly His Ser Phe Arg Gly Arg Leu Ser Ser Arg Arg Ser Leu Ser Ala
 225 230 235 240
 Ser Thr Glu Val Pro Ala Ser Phe His Ser Glu Arg Gln Arg Arg Lys
 245 250 255
 5 Ser Ser Leu Met Phe Ser Ser Arg Thr Lys Met Asn Ser Asn Thr Ile
 260 265 270
 Ala Ser Lys Met Gly Ser Phe Ser Gln Ser Asp Ser Val Ala Leu His
 275 280 285
 10 Gln Arg Glu His Val Glu Leu Leu Arg Ala Arg Arg Leu Ala Lys Ser
 290 295 300
 Leu Ala Ile Leu Leu Gly Val Phe Ala Val Cys Trp Ala Pro Tyr Ser
 305 310 315 320
 Leu Phe Thr Ile Val Leu Ser Phe Tyr Ser Ser Ala Thr Gly Pro Lys
 325 330 335
 15 Ser Val Trp Tyr Arg Ile Ala Phe Trp Leu Gln Trp Phe Asn Ser Phe
 340 345 350
 Val Asn Pro Leu Leu Tyr Pro Leu Cys His Lys Arg Phe Gln Lys Ala
 355 360 365
 20 Phe Leu Lys Ile Phe Cys Ile Lys Lys Gln Pro Leu Pro Ser Gln His
 370 375 380
 Ser Arg Ser Val Ser Ser
 385 390

(16) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
 25 (A) LENGTH: 1128 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATGGCGAACG CGAGCGAGCC GGGTGGCAGC GGCGGCGGCG AGGCGGCCGC CCTGGGCCTC 60
 AAGCTGGCCA CGCTCAGCCT GCTGCTGTGC GTGAGCCTAG CGGGCAACGT GCTGTTGCGG 120
 CTGCTGATCG TGCGGGAGCG CAGCCTGCAC CGCGCCCCGT ACTACCTGCT GCTCGACCTG 180
 TGCCTGGCCG ACGGGCTGCG CGCGCTCGCC TGCCTCCCGG CCGTCATGCT GGCGGCGCGG 240
 35 CGTGCGGCGG CCGCGGCGGG GGCGCCGCCG GGCGCGCTGG GCTGCAAGCT GCTCGCCTTC 300

- 20 -

CTGGCCGCGC TCTTCTGCTT CCACGCCGCC TTCCTGCTGC TGGGCGTGGG CGTCACCCGC 360
TACCTGGCCA TCGCGCACCA CCGCTTCTAT GCAGAGCGCC TGGCCGGCTG GCCGTGCGCC 420
GCCATGCTGG TGTGCGCCGC CTGGGCGCTG GCGCTGGCCG CGGCCTTCCC GCCAGTGCTG 480
GACGGCGGTG GCGACGACGA GGACGCGCCG TCGCCCTGG AGCAGCGGCC CGACGGCGCC 540
5 CCCGGCGCGC TGGGCTTCCT GCTGCTGCTG GCCGTGGTGG TGGGCGCCAC GCACCTCGTC 600
TACCTCCGCC TGCTCTTCTT CATCCACGAC CGCCGCAAGA TCGGGCCCGC GCGCCTGGTG 660
CCCGCCGTCA GCCACGACTG GACCTTCCAC GGCCCGGGCG CCACCGGCCA GGCGGCCGCC 720
AACTGGACGG CGGGCTTCGG CCGCGGGCCC ACGCCGCCCG CGCTTGTGGG CATCCGGCCC 780
GCAGGGCCGG GCCGCGGCGC GCGCCGCCTC CTCGTGCTGG AAGAATTCAA GACGGAGAAG 840
10 AGGCTGTGCA AGATGTTCTA CGCCGTCACG CTGCTCTTCC TGCTCCTCTG GGGGCCCTAC 900
GTCGTGGCCA GCTACCTGCG GGTCTGGTG CGGCCCGGCG CCGTCCCCCA GGCCTACCTG 960
ACGGCCTCCG TGTGGCTGAC CTTGCGCAG GCCGGCATCA ACCCCGTCGT GTGCTTCCTC1020
TTCAACAGGG AGCTGAGGGA CTGCTTCAGG GCCAGTTCC CCTGCTGCCA GAGCCCCCGG1080
ACCACCCAGG CGACCCATCC CTGCGACCTG AAAGGCATTG GTTTATGA 1128

15 (17) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 375 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
20 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ala Asn Ala Ser Glu Pro Gly Gly Ser Gly Gly Gly Glu Ala Ala
1 5 10 15
25 Ala Leu Gly Leu Lys Leu Ala Thr Leu Ser Leu Leu Leu Cys Val Ser
20 25 30
Leu Ala Gly Asn Val Leu Phe Ala Leu Leu Ile Val Arg Glu Arg Ser
35 40 45
30 Leu His Arg Ala Pro Tyr Tyr Leu Leu Leu Asp Leu Cys Leu Ala Asp
50 55 60
Gly Leu Arg Ala Leu Ala Cys Leu Pro Ala Val Met Leu Ala Ala Arg
65 70 75 80

- 21 -

Arg Ala Ala Ala Ala Gly Ala Pro Pro Gly Ala Leu Gly Cys Lys
 85 90 95

Leu Leu Ala Phe Leu Ala Ala Leu Phe Cys Phe His Ala Ala Phe Leu
 100 105 110

5 Leu Leu Gly Val Gly Val Thr Arg Tyr Leu Ala Ile Ala His His Arg
 115 120 125

Phe Tyr Ala Glu Arg Leu Ala Gly Trp Pro Cys Ala Ala Met Leu Val
 130 135 140

10 Cys Ala Ala Trp Ala Leu Ala Leu Ala Ala Ala Phe Pro Pro Val Leu
 145 150 155 160

Asp Gly Gly Gly Asp Asp Glu Asp Ala Pro Cys Ala Leu Glu Gln Arg
 165 170 175

Pro Asp Gly Ala Pro Gly Ala Leu Gly Phe Leu Leu Leu Leu Ala Val
 180 185 190

15 Val Val Gly Ala Thr His Leu Val Tyr Leu Arg Leu Leu Phe Phe Ile
 195 200 205

His Asp Arg Arg Lys Met Arg Pro Ala Arg Leu Val Pro Ala Val Ser
 210 215 220

20 His Asp Trp Thr Phe His Gly Pro Gly Ala Thr Gly Gln Ala Ala Ala
 225 230 235 240

Asn Trp Thr Ala Gly Phe Gly Arg Gly Pro Thr Pro Pro Ala Leu Val
 245 250 255

Gly Ile Arg Pro Ala Gly Pro Gly Arg Gly Ala Arg Arg Leu Leu Val
 260 265 270

25 Leu Glu Glu Phe Lys Thr Glu Lys Arg Leu Cys Lys Met Phe Tyr Ala
 275 280 285

Val Thr Leu Leu Phe Leu Leu Leu Trp Gly Pro Tyr Val Val Ala Ser
 290 295 300

30 Tyr Leu Arg Val Leu Val Arg Pro Gly Ala Val Pro Gln Ala Tyr Leu
 305 310 315 320

Thr Ala Ser Val Trp Leu Thr Phe Ala Gln Ala Gly Ile Asn Pro Val
 325 330 335

Val Cys Phe Leu Phe Asn Arg Glu Leu Arg Asp Cys Phe Arg Ala Gln
 340 345 350

35 Phe Pro Cys Cys Gln Ser Pro Arg Thr Thr Gln Ala Thr His Pro Cys
 355 360 365

Asp Leu Lys Gly Ile Gly Leu

- 22 -

370

375

(18) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1002 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

10 ATGAACACCA CAGTGATGCA AGGCTTCAAC AGATCTGAGC GGTGCCCCAG AGACACTCGG 60
ATAGTACAGC TGGTATTCCC AGCCCTCTAC ACAGTGTTTT TCTTGACCGG CATCCTGCTG 120
AATACTTTGG CTCTGTGGGT GTTTGTTTAC ATCCCCAGCT CCTCCACCTT CATCATCTAC 180
CTCAAAAACA CTTTGGTGGC CGACTTGATA ATGACACTCA TGCTTCCTTT CAAAATCCTC 240
TCTGACTCAC ACCTGGCACC CTGGCAGCTC AGAGCTTTTG TGTGTCGTTT TTCTTCGGTG 300
15 ATATTTTATG AGACCATGTA TGTGGGCATC GTGCTGTTAG GGCTCATAGC CTTTGACAGA 360
TTCCTCAAGA TCATCAGACC TTTGAGAAAT ATTTTCTAA AAAACCTGT TTTGCAAAA 420
ACGGTCTCAA TCTTCATCTG GTTCTTTTTG TTCTTCATCT CCCTGCCAAA TACGATCTTG 480
AGCAACAAGG AAGCAACACC ATCGTCTGTG AAAAAGTGTG CTTCTTAAA GGGGCCTCTG 540
GGGCTGAAAT GGCATCAAAT GGTAATAAC ATATGCCAGT TTATTTTCTG GACTGTTTTT 600
20 ATCCTAATGC TTGTGTTTTA TGTGGTTATT GCAAAAAAG TATATGATTC TTATAGAAAG 660
TCCAAAAGTA AGGACAGAAA AAACAACAAA AAGCTGGAAG GCAAAGTATT TGTTGTCGTG 720
GCTGTCTTCT TTGTGTGTTT TGCTCCATTT CATTTTGCCA GAGTTCCATA TACTCACAGT 780
CAAACCAACA ATAAGACTGA CTGTAGACTG CAAAATCAAC TGTTTATTGC TAAAGAAACA 840
ACTCTCTTTT TGGCAGCAAC TAACATTTGT ATGGATCCCT TAATATACAT ATTCTTATGT 900
25 AAAAAATTCA CAGAAAAGCT ACCATGTATG CAAGGGAGAA AGACCACAGC ATCAAGCCAA 960
-GAAAATCATA GCAGTCAGAC AGACAACATA ACCTTAGGCT GA 1002

(19) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 333 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

- 23 -

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

5 Met Asn Thr Thr Val Met Gln Gly Phe Asn Arg Ser Glu Arg Cys Pro
 1 5 10 15
 Arg Asp Thr Arg Ile Val Gln Leu Val Phe Pro Ala Leu Tyr Thr Val
 20 25 30
 Val Phe Leu Thr Gly Ile Leu Leu Asn Thr Leu Ala Leu Trp Val Phe
 35 40 45
 10 Val His Ile Pro Ser Ser Ser Thr Phe Ile Ile Tyr Leu Lys Asn Thr
 50 55 60
 Leu Val Ala Asp Leu Ile Met Thr Leu Met Leu Pro Phe Lys Ile Leu
 65 70 75 80
 15 Ser Asp Ser His Leu Ala Pro Trp Gln Leu Arg Ala Phe Val Cys Arg
 85 90 95
 Phe Ser Ser Val Ile Phe Tyr Glu Thr Met Tyr Val Gly Ile Val Leu
 100 105 110
 Leu Gly Leu Ile Ala Phe Asp Arg Phe Leu Lys Ile Ile Arg Pro Leu
 115 120 125
 20 Arg Asn Ile Phe Leu Lys Lys Pro Val Phe Ala Lys Thr Val Ser Ile
 130 135 140
 Phe Ile Trp Phe Phe Leu Phe Phe Ile Ser Leu Pro Asn Thr Ile Leu
 145 150 155 160
 25 Ser Asn Lys Glu Ala Thr Pro Ser Ser Val Lys Lys Cys Ala Ser Leu
 165 170 175
 Lys Gly Pro Leu Gly Leu Lys Trp His Gln Met Val Asn Asn Ile Cys
 180 185 190
 Gln Phe Ile Phe Trp Thr Val Phe Ile Leu Met Leu Val Phe Tyr Val
 195 200 205
 30 Val Ile Ala Lys Lys Val Tyr Asp Ser Tyr Arg Lys Ser Lys Ser Lys
 210 215 220
 Asp Arg Lys Asn Asn Lys Lys Leu Glu Gly Lys Val Phe Val Val Val
 225 230 235 240
 35 Ala Val Phe Phe Val Cys Phe Ala Pro Phe His Phe Ala Arg Val Pro
 245 250 255

- 24 -

Tyr Thr His Ser Gln Thr Asn Asn Lys Thr Asp Cys Arg Leu Gln Asn
 260 265 270

 Gln Leu Phe Ile Ala Lys Glu Thr Thr Leu Phe Leu Ala Ala Thr Asn
 275 280 285

 5 Ile Cys Met Asp Pro Leu Ile Tyr Ile Phe Leu Cys Lys Lys Phe Thr
 290 295 300

 Glu Lys Leu Pro Cys Met Gln Gly Arg Lys Thr Thr Ala Ser Ser Gln
 305 310 315 320

 10 Glu Asn His Ser Ser Gln Thr Asp Asn Ile Thr Leu Gly
 325 330

(20) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1122 base pairs
 (B) TYPE: nucleic acid
 15 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ATGGCCAACA CTACCGGAGA GCCTGAGGAG GTGAGCGGCG CTCTGTCCCC ACCGTCCGCA 60
 20 TCAGCTTATG TGAAGCTGGT ACTGCTGGGA CTGATTATGT GCGTGAGCCT GGC GG GTAAC 120
 GCCATCTTGT CCCTGCTGGT GCTCAAGGAG CGTGCCCTGC ACAAGGCTCC TTA C TACTTC 180
 CTGCTGGACC TGTGCCTGGC CGATGGCATA CGCTCTGCCG TCTGCTTCCC CTTTGTGCTG 240
 GCTTCTGTGC GCCACGGCTC TTCATGGACC TTCAGTGCAC TCAGCTGCAA GATTGTGGCC 300
 TTTATGGCCG TGCTCTTTTG CTTCCATGCG GCCTTCATGC TGTTCTGCAT CAGCGTCACC 360
 25 CGCTACATGG CCATCGCCCA CCACCGCTTC TACGCCAAGC GCATGACACT CTGGACATGC 420
 GCGGCTGTCA TCTGCATGGC CTGGACCCTG TCTGTGGCCA TGGCCTTCCC ACCTGTCTTT 480
 GACGTGGGCA CCTACAAGTT TATTCGGGAG GAGGACCACT GCATCTTTGA GCATCGCTAC 540
 TTCAAGGCCA ATGACACGCT GGGCTTCATG CTTATGTTGG CTGTGCTCAT GGCAGCTACC 600
 CATGCTGTCT ACGGCAAGCT GCTCCTCTTC GAGTATCGTC ACCGCAAGAT GAAGCCAGTG 660
 30 CAGATGGTGC CAGCCATCAG CCAGAACTGG ACATTCCATG GTCCCGGGGC CACCGGCCAG 720
 GCTGCTGCCA ACTGGATCGC CGGCTTTGGC CGTGGGCCCCA TGCCACCAAC CCTGCTGGGT 780
 ATCCGGCAGA ATGGGCATGC AGCCAGCCGG CGGCTACTGG GCATGGACGA GGTC AAGGGT 840

- 25 -

GAAAAGCAGC TGGGCCGCAT GTTCTACGCG ATCACACTGC TCTTTCTGCT CCTCTGGTCA 900
 CCCTACATCG TGGCCTGCTA CTGGCGAGTG TTTGTGAAAG CCTGTGCTGT GCCCCACCGC 960
 TACCTGGCCA CTGCTGTTTG GATGAGCTTC GCCCAGGCTG CCGTCAACCC AATTGTCTGC1020
 TTCCTGCTCA ACAAGGACCT CAAGAAGTGC CTGACCACTC ACGCCCCCTG CTGGGGCACA1080
 5 GGAGGTGCCC CGGCTCCCAG AGAACCTAC TGTGTCATGT GA 1122

(21) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 373 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

15 Met Ala Asn Thr Thr Gly Glu Pro Glu Glu Val Ser Gly Ala Leu Ser
 1 5 10 15
 Pro Pro Ser Ala Ser Ala Tyr Val Lys Leu Val Leu Leu Gly Leu Ile
 20 20 25 30
 Met Cys Val Ser Leu Ala Gly Asn Ala Ile Leu Ser Leu Leu Val Leu
 35 40 45
 20 Lys Glu Arg Ala Leu His Lys Ala Pro Tyr Tyr Phe Leu Leu Asp Leu
 50 55 60
 Cys Leu Ala Asp Gly Ile Arg Ser Ala Val Cys Phe Pro Phe Val Leu
 65 70 75 80
 25 Ala Ser Val Arg His Gly Ser Ser Trp Thr Phe Ser Ala Leu Ser Cys
 85 90 95
 Lys Ile Val Ala Phe Met Ala Val Leu Phe Cys Phe His Ala Ala Phe
 100 105 110
 Met Leu Phe Cys Ile Ser Val Thr Arg Tyr Met Ala Ile Ala His His
 115 120 125
 - 30 Arg Phe Tyr Ala Lys Arg Met Thr Leu Trp Thr Cys Ala Ala Val Ile
 130 135 140
 Cys Met Ala Trp Thr Leu Ser Val Ala Met Ala Phe Pro Pro Val Phe
 145 150 155 160
 35 Asp Val Gly Thr Tyr Lys Phe Ile Arg Glu Glu Asp Gln Cys Ile Phe
 165 170 175

- 26 -

Glu His Arg Tyr Phe Lys Ala Asn Asp Thr Leu Gly Phe Met Leu Met
 180 185 190
 Leu Ala Val Leu Met Ala Ala Thr His Ala Val Tyr Gly Lys Leu Leu
 195 200 205
 5 Leu Phe Glu Tyr Arg His Arg Lys Met Lys Pro Val Gln Met Val Pro
 210 215 220
 Ala Ile Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala Thr Gly Gln
 225 230 235 240
 10 Ala Ala Ala Asn Trp Ile Ala Gly Phe Gly Arg Gly Pro Met Pro Pro
 245 250 255
 Thr Leu Leu Gly Ile Arg Gln Asn Gly His Ala Ala Ser Arg Arg Leu
 260 265 270
 Leu Gly Met Asp Glu Val Lys Gly Glu Lys Gln Leu Gly Arg Met Phe
 275 280 285
 15 Tyr Ala Ile Thr Leu Leu Phe Leu Leu Leu Trp Ser Pro Tyr Ile Val
 290 295 300
 Ala Cys Tyr Trp Arg Val Phe Val Lys Ala Cys Ala Val Pro His Arg
 305 310 315 320
 20 Tyr Leu Ala Thr Ala Val Trp Met Ser Phe Ala Gln Ala Ala Val Asn
 325 330 335
 Pro Ile Val Cys Phe Leu Leu Asn Lys Asp Leu Lys Lys Cys Leu Thr
 340 345 350
 Thr His Ala Pro Cys Trp Gly Thr Gly Gly Ala Pro Ala Pro Arg Glu
 355 360 365
 25 Pro Tyr Cys Val Met
 370

(22) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 1053 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

35 ATGGCTTTGG AACAGAACCA GTCAACAGAT TATTATTATG AGGAAAATGA AATGAATGGC 60
 ACTTATGACT ACAGTCAATA TGAATTGATC TGTATCAAAG AAGATGTCAG AGAATTTGCA 120

- 27 -

AAAGTTTTCC TCCCTGTATT CCTCACAATA GCTTTCGTCA TTGGACTTGC AGGCAATTCC 180
 ATGGTAGTGG CAATTTATGC CTATTACAAG AAACAGAGAA CCAAAACAGA TGTGTACATC 240
 CTGAATTTGG CTGTAGCAGA TTTACTCCTT CTATTCACCTC TGCCTTTTTG GGCTGTTAAT 300
 GCAGTTCATG GGTGGGTTTT AGGGAAAATA ATGTGCAAAA TAACTTCAGC CTTGTACACA 360
 5 CTAAACTTTG TCTCTGGAAT GCAGTTTCTG GCTTGCATCA GCATAGACAG ATATGTGGCA 420
 GTAACATAATG TCCCCAGCCA ATCAGGAGTG GGAAAACCAT GCTGGATCAT CTGTTTCTGT 480
 GTCTGGATGG CTGCCATCTT GCTGAGCATA CCCCAGCTGG TTTTTTATAC AGTAAATGAC 540
 AATGCTAGGT GCATTCCCAT TTTCCCCCGC TACCTAGGAA CATCAATGAA AGCATTGATT 600
 CAAATGCTAG AGATCTGCAT TGGATTTGTA GTACCCTTTC TTATTATGGG GGTGTGCTAC 660
 10 TTTATCACGG CAAGGACACT CATGAAGATG CCAAACATTA AAATATCTCG ACCCCTAAAA 720
 GTTCTGCTCA CAGTCGTTAT AGTTTTCAAT GTCACTCAAC TGCCTTATAA CATTGTCAAG 780
 TTCTGCCGAG CCATAGACAT CATCTACTCC CTGATCACCA GCTGCAACAT GAGCAAACGC 840
 ATGGACATCG CCATCCAAGT CACAGAAAGC ATTGCACTCT TTCACAGCTG CCTCAACCCA 900
 ATCCTTTATG TTTTTATGGG AGCATCTTTC AAAAAGTACG TTATGAAAGT GGCCAAGAAA 960
 15 TATGGGTCCT GGAGAAGACA GAGACAAAGT GTGGAGGAGT TTCCTTTTGA TTCTGAGGGT 1020
 CCTACAGAGC CAACCAAGTAC TTTTAGCATT TAA 1053

(23) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 350 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

25 Met Ala Leu Glu Gln Asn Gln Ser Thr Asp Tyr Tyr Tyr Glu Glu Asn
 1 5 10 15
 Glu Met Asn Gly Thr Tyr Asp Tyr Ser Gln Tyr Glu Leu Ile Cys Ile
 20 25 30
 30 Lys Glu Asp Val Arg Glu Phe Ala Lys Val Phe Leu Pro Val Phe Leu
 35 40 45
 Thr Ile Ala Phe Val Ile Gly Leu Ala Gly Asn Ser Met Val Val Ala

- 28 -

	50	55	60
	Ile Tyr Ala Tyr Tyr Lys Lys Gln Arg Thr Lys Thr Asp Val Tyr Ile 65 70 75 80		
5	Leu Asn Leu Ala Val Ala Asp Leu Leu Leu Leu Phe Thr Leu Pro Phe 85 90 95		
	Trp Ala Val Asn Ala Val His Gly Trp Val Leu Gly Lys Ile Met Cys 100 105 110		
	Lys Ile Thr Ser Ala Leu Tyr Thr Leu Asn Phe Val Ser Gly Met Gln 115 120 125		
10	Phe Leu Ala Cys Ile Ser Ile Asp Arg Tyr Val Ala Val Thr Asn Val 130 135 140		
	Pro Ser Gln Ser Gly Val Gly Lys Pro Cys Trp Ile Ile Cys Phe Cys 145 150 155 160		
15	Val Trp Met Ala Ala Ile Leu Leu Ser Ile Pro Gln Leu Val Phe Tyr 165 170 175		
	Thr Val Asn Asp Asn Ala Arg Cys Ile Pro Ile Phe Pro Arg Tyr Leu 180 185 190		
	Gly Thr Ser Met Lys Ala Leu Ile Gln Met Leu Glu Ile Cys Ile Gly 195 200 205		
20	Phe Val Val Pro Phe Leu Ile Met Gly Val Cys Tyr Phe Ile Thr Ala 210 215 220		
	Arg Thr Leu Met Lys Met Pro Asn Ile Lys Ile Ser Arg Pro Leu Lys 225 230 235 240		
25	Val Leu Leu Thr Val Val Ile Val Phe Ile Val Thr Gln Leu Pro Tyr 245 250 255		
	Asn Ile Val Lys Phe Cys Arg Ala Ile Asp Ile Ile Tyr Ser Leu Ile 260 265 270		
	Thr Ser Cys Asn Met Ser Lys Arg Met Asp Ile Ala Ile Gln Val Thr 275 280 285		
30	Glu Ser Ile Ala Leu Phe His Ser Cys Leu Asn Pro Ile Leu Tyr Val 290 295 300		
	Phe Met Gly Ala Ser Phe Lys Asn Tyr Val Met Lys Val Ala Lys Lys 305 310 315 320		
35	Tyr Gly Ser Trp Arg Arg Gln Arg Gln Ser Val Glu Glu Phe Pro Phe 325 330 335		
	Asp Ser Glu Gly Pro Thr Glu Pro Thr Ser Thr Phe Ser Ile 340 345 350		

- 29 -

(24) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1116 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ATGCCAGGAA ACGCCACCCC AGTGACCACC ACTGCCCCGT GGGCCTCCCT GGGCCTCTCC 60
10 GCCAAGACCT GCAACAACGT GTCCTTCGAA GAGAGCAGGA TAGTCCTGGT CGTGGTGTAC 120
AGCGCGGTGT GCACGCTGGG GGTGCCGGCC AACTGCCTGA CTGCGTGGCT GGCCTGCTG 180
CAGGTACTGC AGGGCAACGT GCTGGCCGTC TACCTGCTCT GCCTGGCACT CTGCGAAGCTG 240
CTGTACACAG GCACGCTGCC ACTCTGGGTC ATCTATATCC GCAACCAGCA CCGCTGGACC 300
CTAGGCCTGC TGGCCTCGAA GGTGACCGCC TACATCTTCT TCTGCAACAT CTACGTCAGC 360
15 ATCCTCTTCC TGTGCTGCAT CTCCTGCGAC CGCTTCGTGG CCGTGGTGTA CGCGCTGGAG 420
AGTCGGGGCC GCCGCCGCCG GAGGACCGCC ATCCTCATCT CCGCCTGCAT CTTTCATCTC 480
GTCGGGATCG TTTACTACCC GGTGTTCCAG ACGGAAGACA AGGAGACCTG CTTTGACATG 540
CTGCAGATGG ACAGCAGGAT TGCCGGGTAC TACTACGCCA GGTTCACCGT TGGCTTTGCC 600
ATCCCTCTCT CCATCATCGC CTTACCAAC CACCGGATTT TCAGGAGCAT CAAGCAGAGC 660
20 ATGGGCTTAA GCGCTGCCCA GAAGGCCAAG GTGAAGCACT CGGCCATCGC GGTGGTTGTC 720
ATCTTCCTAG TCTGCTTCGC CCCGTACCAC CTGGTTCTCC TCGTCAAAGC CGCTGCCTTT 780
TCCTACTACA GAGGAGACAG GAACGCCATG TGCGGCTTGG AGGAAAGGCT GTACACAGCC 840
TCTGTGGTGT TTCTGTGCCT GTCCACGGTG AACGGCGTGG CTGACCCCAT TATCTACGTG 900
CTGGCCACGG ACCATTCCCG CCAAGAAGTG TCCAGAATCC ATAAGGGGTG GAAAGAGTGG 960
25 TCCATGAAGA CAGACGTCAC CAGGCTCACC CACAGCAGGG ACACCGAGGA GCTGCAGTCG 1020
CCCGTGGCCC TTGCAGACCA CTACACCTTC TCCAGGCCCG TGCACCCACC AGGGTCACCA 1080
TGCCCTGCAA AGAGGCTGAT TGAGGAGTCC TGCTGA 1116

(25) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 371 amino acids

- 30 -

- (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Pro Gly Asn Ala Thr Pro Val Thr Thr Thr Ala Pro Trp Ala Ser
 1 5 10 15

Leu Gly Leu Ser Ala Lys Thr Cys Asn Asn Val Ser Phe Glu Glu Ser
 20 25 30

10 Arg Ile Val Leu Val Val Val Tyr Ser Ala Val Cys Thr Leu Gly Val
 35 40 45

Pro Ala Asn Cys Leu Thr Ala Trp Leu Ala Leu Leu Gln Val Leu Gln
 50 55 60

15 Gly Asn Val Leu Ala Val Tyr Leu Leu Cys Leu Ala Leu Cys Glu Leu
 65 70 75 80

Leu Tyr Thr Gly Thr Leu Pro Leu Trp Val Ile Tyr Ile Arg Asn Gln
 85 90 95

His Arg Trp Thr Leu Gly Leu Leu Ala Ser Lys Val Thr Ala Tyr Ile
 100 105 110

20 Phe Phe Cys Asn Ile Tyr Val Ser Ile Leu Phe Leu Cys Cys Ile Ser
 115 120 125

Cys Asp Arg Phe Val Ala Val Val Tyr Ala Leu Glu Ser Arg Gly Arg
 130 135 140

25 Arg Arg Arg Arg Thr Ala Ile Leu Ile Ser Ala Cys Ile Phe Ile Leu
 145 150 155 160

Val Gly Ile Val His Tyr Pro Val Phe Gln Thr Glu Asp Lys Glu Thr
 165 170 175

Cys Phe Asp Met Leu Gln Met Asp Ser Arg Ile Ala Gly Tyr Tyr Tyr
 180 185 190

30 Ala Arg Phe Thr Val Gly Phe Ala Ile Pro Leu Ser Ile Ile Ala Phe
 195 200 205

Thr Asn His Arg Ile Phe Arg Ser Ile Lys Gln Ser Met Gly Leu Ser
 210 215 220

35 Ala Ala Gln Lys Ala Lys Val Lys His Ser Ala Ile Ala Val Val Val
 225 230 235 240

- 31 -

Ile Phe Leu Val Cys Phe Ala Pro Tyr His Leu Val Leu Leu Val Lys
 245 250 255

Ala Ala Ala Phe Ser Tyr Tyr Arg Gly Asp Arg Asn Ala Met Cys Gly
 260 265 270

5 Leu Glu Glu Arg Leu Tyr Thr Ala Ser Val Val Phe Leu Cys Leu Ser
 275 280 285

Thr Val Asn Gly Val Ala Asp Pro Ile Ile Tyr Val Leu Ala Thr Asp
 290 295 300

10 His Ser Arg Gln Glu Val Ser Arg Ile His Lys Gly Trp Lys Glu Trp
 305 310 315 320

Ser Met Lys Thr Asp Val Thr Arg Leu Thr His Ser Arg Asp Thr Glu
 325 330 335

Glu Leu Gln Ser Pro Val Ala Leu Ala Asp His Tyr Thr Phe Ser Arg
 340 345 350

15 Pro Val His Pro Pro Gly Ser Pro Cys Pro Ala Lys Arg Leu Ile Glu
 355 360 365

Glu Ser Cys
 370

(26) INFORMATION FOR SEQ ID NO:25:

- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1113 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

ATGGCGAACT ATAGCCATGC AGCTGACAAC ATTTTGCAAA ATCTCTCGCC TCTAACAGCC 60
 TTTCTGAAAC TGAATTCCTT GGGTTTCATA ATAGGAGTCA GCGTGGTGGG CAACCTCCTG 120
 ATCTCCATTT TGCTAGTGAA AGATAAGACC TTGCATAGAG CACCTTACTA CTTCTGTGTT 180
 30 GATCTTTGCT GTTCAGATAT CCTCAGATCT GCAATTTGTT TCCCATTTGT GTTCAACTCT 240
 GTCAAAAATG GCTCTACCTG GACTTATGGG ACTCTGACTT GCAAAGTGAT TGCCTTTCTG 300
 GGGGTTTTGT CCTGTTTCCA CACTGCTTTC ATGCTCTTCT GCATCAGTGT CACCAGATAC 360
 TTAGCTATCG CCCATCACCG CTTCTATACA AAGAGGCTGA CCTTTTGGAC GTGTCTGGCT 420
 GTGATCTGTA TGGTGTGGAC TCTGTCTGTG GCCATGGCAT TTCCCCGGT TTTAGACGTG 480

- 32 -

GGCACTTACT CATTCAATTAG GGAGGAAGAT CAATGCACCT TCCAACACCG CTCCTTCAGG 540
 GCTAATGATT CCTTAGGATT TATGCTGCTT CTTGCTCTCA TCCTCCTAGC CACACAGCTT 600
 GTCTACCTCA AGCTGATATT TTTCGTCCAC GATCGAAGAA AAATGAAGCC AGTCCAGTTT 660
 GTAGCAGCAG TCAGCCAGAA CTGGACTTTT CATGGTCCTG GAGCCAGTGG CCAGGCAGCT 720
 5 GCCAATTGGC TAGCAGGATT TGGAAGGGGT CCCACACCAC CCACCTTGCT GGGCATCAGG 780
 CAAAATGCAA ACACCACAGG CAGAAGAAGG CTATTGGTCT TAGACGAGTT CAAAATGGAG 840
 AAAAGAATCA GCAGAATGTT CTATATAATG ACTTTTCTGT TTCTAACCTT GTGGGGCCCC 900
 TACCTGGTGG CCTGTTATTG GAGAGTTTTT GCAAGAGGGC CTGTAGTACC AGGGGGATTT 960
 CTAACAGCTG CTGTCTGGAT GAGTTTTGCC CAAGCAGGAA TCAATCCTTT TGTCTGCATT1020
 10 TTCTCAAACA GGGAGCTGAG GCGCTGTTTC AGCACAACCC TTCTTTACTG CAGAAAATCC1080
 AGGTTACCAA GGGAACCTTA CTGTGTTATA TGA 1113

(27) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 370 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

20 Met Ala Asn Tyr Ser His Ala Ala Asp Asn Ile Leu Gln Asn Leu Ser
 1 5 10 15
 Pro Leu Thr Ala Phe Leu Lys Leu Thr Ser Leu Gly Phe Ile Ile Gly
 20 25 30
 25 Val Ser Val Val Gly Asn Leu Leu Ile Ser Ile Leu Leu Val Lys Asp
 35 40 45
 Lys Thr Leu His Arg Ala Pro Tyr Tyr Phe Leu Leu Asp Leu Cys Cys
 50 55 60
 Ser Asp Ile Leu Arg Ser Ala Ile Cys Phe Pro Phe Val Phe Asn Ser
 65 70 75 80
 30 Val Lys Asn Gly Ser Thr Trp Thr Tyr Gly Thr Leu Thr Cys Lys Val
 85 90 95
 Ile Ala Phe Leu Gly Val Leu Ser Cys Phe His Thr Ala Phe Met Leu

- 33 -

	100	105	110
	Phe Cys Ile Ser Val Thr Arg Tyr Leu Ala Ile Ala His His Arg Phe 115 120 125		
5	Tyr Thr Lys Arg Leu Thr Phe Trp Thr Cys Leu Ala Val Ile Cys Met 130 135 140		
	Val Trp Thr Leu Ser Val Ala Met Ala Phe Pro Pro Val Leu Asp Val 145 150 155 160		
	Gly Thr Tyr Ser Phe Ile Arg Glu Glu Asp Gln Cys Thr Phe Gln His 165 170 175		
10	Arg Ser Phe Arg Ala Asn Asp Ser Leu Gly Phe Met Leu Leu Leu Ala 180 185 190		
	Leu Ile Leu Leu Ala Thr Gln Leu Val Tyr Leu Lys Leu Ile Phe Phe 195 200 205		
15	Val His Asp Arg Arg Lys Met Lys Pro Val Gln Phe Val Ala Ala Val 210 215 220		
	Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala Ser Gly Gln Ala Ala 225 230 235 240		
	Ala Asn Trp Leu Ala Gly Phe Gly Arg Gly Pro Thr Pro Pro Thr Leu 245 250 255		
20	Leu Gly Ile Arg Gln Asn Ala Asn Thr Thr Gly Arg Arg Arg Leu Leu 260 265 270		
	Val Leu Asp Glu Phe Lys Met Glu Lys Arg Ile Ser Arg Met Phe Tyr 275 280 285		
25	Ile Met Thr Phe Leu Phe Leu Thr Leu Trp Gly Pro Tyr Leu Val Ala 290 295 300		
	Cys Tyr Trp Arg Val Phe Ala Arg Gly Pro Val Val Pro Gly Gly Phe 305 310 315 320		
	Leu Thr Ala Ala Val Trp Met Ser Phe Ala Gln Ala Gly Ile Asn Pro 325 330 335		
30	Phe Val Cys Ile Phe Ser Asn Arg Glu Leu Arg Arg Cys Phe Ser Thr 340 345 350		
	Thr Leu Leu Tyr Cys Arg Lys Ser Arg Leu Pro Arg Glu Pro Tyr Cys 355 360 365		
35	Val Ile 370		

(28) INFORMATION FOR SEQ ID NO:27:

- 34 -

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1080 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ATGCAGGTCC CGAACAGCAC CGGCCCGGAC AACGCGACGC TGCAGATGCT GCGGAACCCG 60
GCGATCGCGG TGGCCCTGCC CGTGGTGTAC TCGCTGGTGG CGGCGGTCAG CATCCCGGGC 120
10 AACCTCTTCT CTCTGTGGGT GCTGTGCCGG CGCATGGGGC CCAGATCCCC GTCGGTCATC 180
TTCATGATCA ACCTGAGCGT CACGGACCTG ATGCTGGCCA GCGTGTGGCC TTTCCAAATC 240
TACTACCATT GCAACCGCCA CCACTGGGTA TTCGGGGTGC TGCTTTGCAA CGTGGTGACC 300
GTGGCCTTTT ACGCAAACAT GTATTCCAGC ATCCTCACCA TGACCTGTAT CAGCGTGGAG 360
CGCTTCCTGG GGGTCCTGTA CCCGCTCAGC TCCAAGCGCT GGCGCCGCCG TC GTTACGCG 420
15 GTGGCCGCGT GTGCAGGGAC CTGGCTGCTG CTCCTGACCG CCCTGTGCCC GCTGGCGCGC 480
ACCGATCTCA CCTACCCGGT GCACGCCCTG GGCATCATCA CCTGCTTCGA CGTCCTCAAG 540
TGGACGATGC TCCCAGCGT GGCCATGTGG GCCGTGTTCC TCTTCACCAT CTTCATCCTG 600
CTGTTCTCTA TCCCGTTCGT GATCACCGTG GCTTGTTACA CGGCCACCAT CCTCAAGCTG 660
TTGCGCACGG AGGAGGCGCA CGGCCGGGAG CAGCGGAGGC GCGCGGTGGG CCTGGCCGCG 720
20 GTGGTCTTGC TGGCCTTTGT CACCTGCTTC GCCCCAACA ACTTCGTGCT CCTGGCGCAC 780
ATCGTGAGCC GCCTGTTCTA CGGCAAGAGC TACTACCAG TGTACAAGCT CACGCTGTGT 840
CTCAGCTGCC TCAACAAC TG TCTGGACCCG TTTGTTTATT ACTTTGCGTC CCGGAATTC 900
CAGCTGCGCC TGCGGGAATA TTTGGGCTGC CGCCGGGTGC CCAGAGACAC CCTGGACACG 960
CGCCGCGAGA GCCTCTTCTC CGCCAGGACC ACGTCCGTGC GCTCCGAGGC CGGTGCGCAC 1020
25 CCTGAAGGGA TGGAGGGAGC CACCAGGCCC GGCCTCCAGA GGCAGGAGAG TGTGTTCTGA 1080

(29) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 359 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

- 35 -

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

	Met	Gln	Val	Pro	Asn	Ser	Thr	Gly	Pro	Asp	Asn	Ala	Thr	Leu	Gln	Met	
	1				5				10					15			
5	Leu	Arg	Asn	Pro	Ala	Ile	Ala	Val	Ala	Leu	Pro	Val	Val	Tyr	Ser	Leu	
				20				25					30				
	Val	Ala	Ala	Val	Ser	Ile	Pro	Gly	Asn	Leu	Phe	Ser	Leu	Trp	Val	Leu	
			35					40					45				
10	Cys	Arg	Arg	Met	Gly	Pro	Arg	Ser	Pro	Ser	Val	Ile	Phe	Met	Ile	Asn	
	50					55					60						
	Leu	Ser	Val	Thr	Asp	Leu	Met	Leu	Ala	Ser	Val	Leu	Pro	Phe	Gln	Ile	
	65				70				75				80				
	Tyr	Tyr	His	Cys	Asn	Arg	His	His	Trp	Val	Phe	Gly	Val	Leu	Leu	Cys	
				85					90					95			
15	Asn	Val	Val	Thr	Val	Ala	Phe	Tyr	Ala	Asn	Met	Tyr	Ser	Ser	Ile	Leu	
				100					105					110			
	Thr	Met	Thr	Cys	Ile	Ser	Val	Glu	Arg	Phe	Leu	Gly	Val	Leu	Tyr	Pro	
			115				120					125					
20	Leu	Ser	Ser	Lys	Arg	Trp	Arg	Arg	Arg	Arg	Tyr	Ala	Val	Ala	Ala	Cys	
	130					135					140						
	Ala	Gly	Thr	Trp	Leu	Leu	Leu	Leu	Thr	Ala	Leu	Cys	Pro	Leu	Ala	Arg	
	145				150				155					160			
	Thr	Asp	Leu	Thr	Tyr	Pro	Val	His	Ala	Leu	Gly	Ile	Ile	Thr	Cys	Phe	
				165				170					175				
25	Asp	Val	Leu	Lys	Trp	Thr	Met	Leu	Pro	Ser	Val	Ala	Met	Trp	Ala	Val	
			180				185						190				
	Phe	Leu	Phe	Thr	Ile	Phe	Ile	Leu	Leu	Phe	Leu	Ile	Pro	Phe	Val	Ile	
			195				200					205					
30	Thr	Val	Ala	Cys	Tyr	Thr	Ala	Thr	Ile	Leu	Lys	Leu	Leu	Arg	Thr	Glu	
	210					215					220						
	Glu	Ala	His	Gly	Arg	Glu	Gln	Arg	Arg	Arg	Ala	Val	Gly	Leu	Ala	Ala	
	225				230					235				240			
	Val	Val	Leu	Leu	Ala	Phe	Val	Thr	Cys	Phe	Ala	Pro	Asn	Asn	Phe	Val	
				245					250					255			
35	Leu	Leu	Ala	His	Ile	Val	Ser	Arg	Leu	Phe	Tyr	Gly	Lys	Ser	Tyr	Tyr	
			260					265					270				

- 36 -

His Val Tyr Lys Leu Thr Leu Cys Leu Ser Cys Leu Asn Asn Cys Leu
 275 280 285
 Asp Pro Phe Val Tyr Tyr Phe Ala Ser Arg Glu Phe Gln Leu Arg Leu
 290 295 300
 5 Arg Glu Tyr Leu Gly Cys Arg Arg Val Pro Arg Asp Thr Leu Asp Thr
 305 310 315 320
 Arg Arg Glu Ser Leu Phe Ser Ala Arg Thr Thr Ser Val Arg Ser Glu
 325 330 335
 10 Ala Gly Ala His Pro Glu Gly Met Glu Gly Ala Thr Arg Pro Gly Leu
 340 345 350
 Gln Arg Gln Glu Ser Val Phe
 355

(30) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 15 (A) LENGTH: 1503 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ATGGAGCGTC CCTGGGAGGA CAGCCCAGGC CCGGAGGGGG CAGCTGAGGG CTCGCCTGTG 60
 CCAGTCGCCG CCGGGGCGCG CTCCGGTGCC GCGGCGAGTG GCACAGGCTG GCAGCCATGG 120
 GCTGAGTGCC CGGGACCCAA GGGGAGGGGG CAACTGCTGG CGACCGCCGG CCCTTTGCGT 180
 CGCTGGCCCG CCCCCTCGCC TGCCAGCTCC AGCCCCGCCC CCGGAGCGGC GTCCGCTCAC 240
 25 TCGGTTCAAG GCAGCGCGAC TGCGGGTGCC GCACGACCAG GCGCGAGACC TTGGGGCGCG 300
 CGGCCCATGG AGTCGGGGCT GCTGCGGCCG GCGCCGGTGA GCGAGGTCAT CGTCCTGCAT 360
 TACAACTACA CCGGCAAGCT CCGCGGTGCG AGCTACCAGC CGGGTGCCGG CCTGCGCGCC 420
 GACGCCGTGG TGTGCCTGGC GGTGTGCGCC TTCATCGTGC TAGAGAATCT AGCCGTGTTG 480
 TTGGTGCTCG GACGCCACCC GCGCTTCCAC GCTCCCATGT TCCTGCTCCT GGGCAGCCTC 540
 30 ACGTTGTCGG ATCTGCTGGC AGGCGCCGCC TACGCCGCCA ACATCCTACT GTCGGGGCCG 600
 CTCACGCTGA AACTGTCCCC CGCGCTCTGG TTCGCACGGG AGGGAGGCGT CTTCGTGGCA 660
 CTCACTGCGT CCGTGCTGAG CCTCCTGGCC ATCGCGCTGG AGCGCAGCCT CACCATGGCG 720

- 37 -

CGCAGGGGGC CCGCGCCCGT CTCCASTCGG GGGCGCACGC TGGCGATGGC AGCCGCGGCC 780
 TGGGGCGTGT CGCTGCTCCT CGGGCTCCTG CCAGCGCTGG GCTGGAATTG CCTGGGTCGC 840
 CTGGACGCTT GCTCCACTGT CTTGCCGCTC TACGCCAAGG CCTACGTGCT CTTCTGCGTG 900
 CTCGCCTTCG TGGGCATCCT GGCCGCGATC TGTGCACTCT ACGCGCGCAT CTACTGCCAG 960
 5 GTACGCGCCA ACGCGCGGCG CCTGCCGGCA CGGCCCGGGA CTGCGGGGAC CACCTCGACCC1020
 CGGGCGCGTC GCAAGCCGCG CTCTCTGGCC TTGCTGCGCA CGCTCAGCGT GGTGCTCCTG1080
 GCCTTTGTGG CATGTTGGGG CCCCCTCTTC CTGCTGCTGT TGCTCGACGT GGCGTGCCCG1140
 GCGCGCACCT GTCCTGTACT CCTGCAGGCC GATCCCTTCC TGGGACTGGC CATGGCCAAC1200
 TCACTTCTGA ACCCCATCAT CTACACGCTC ACCAACCGCG ACCTGCGCCA CGCGCTCCTG1260
 10 CGCCTGGTCT GCTGCGGACG CCACTCCTGC GGCAGAGACC CGAGTGGCTC CCAGCAGTCG1320
 GCGAGCGCGG CTGAGGCTTC CGGGGGCCTG CGCCGCTGCC TGCCCCCGGG CCTTGATGGG1380
 AGCTTCAGCG GCTCGGAGCG CTCATCGCCC CAGCGCGACG GGCTGGACAC CAGCGGCTCC1440
 ACAGGCAGCC CCGGTGCACC CACAGCCGCC CGGACTCTGG TATCAGAACC GGCTGCAGAC1500
 TGA 1503

15 (31) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 500 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

20 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Glu Arg Pro Trp Glu Asp Ser Pro Gly Pro Glu Gly Ala Ala Glu
 1 5 10 15
 25 Gly Ser Pro Val Pro Val Ala Ala Gly Ala Arg Ser Gly Ala Ala Ala
 20 25 30
 Ser Gly Thr Gly Trp Gln Pro Trp Ala Glu Cys Pro Gly Pro Lys Gly
 35 40 45
 30 Arg Gly Gln Leu Leu Ala Thr Ala Gly Pro Leu Arg Arg Trp Pro Ala
 50 55 60
 Pro Ser Pro Ala Ser Ser Ser Pro Ala Pro Gly Ala Ala Ser Ala His
 65 70 75 80

- 38 -

Ser Val Gln Gly Ser Ala Thr Ala Gly Gly Ala Arg Pro Gly Arg Arg
 85 90 95
 Pro Trp Gly Ala Arg Pro Met Glu Ser Gly Leu Leu Arg Pro Ala Pro
 100 105 110
 5 Val Ser Glu Val Ile Val Leu His Tyr Asn Tyr Thr Gly Lys Leu Arg
 115 120 125
 Gly Ala Ser Tyr Gln Pro Gly Ala Gly Leu Arg Ala Asp Ala Val Val
 130 135 140
 10 Cys Leu Ala Val Cys Ala Phe Ile Val Leu Glu Asn Leu Ala Val Leu
 145 150 155 160
 Leu Val Leu Gly Arg His Pro Arg Phe His Ala Pro Met Phe Leu Leu
 165 170 175
 Leu Gly Ser Leu Thr Leu Ser Asp Leu Leu Ala Gly Ala Ala Tyr Ala
 180 185 190
 15 Ala Asn Ile Leu Leu Ser Gly Pro Leu Thr Leu Lys Leu Ser Pro Ala
 195 200 205
 Leu Trp Phe Ala Arg Glu Gly Gly Val Phe Val Ala Leu Thr Ala Ser
 210 215 220
 20 Val Leu Ser Leu Leu Ala Ile Ala Leu Glu Arg Ser Leu Thr Met Ala
 225 230 235 240
 Arg Arg Gly Pro Ala Pro Val Ser Ser Arg Gly Arg Thr Leu Ala Met
 245 250 255
 Ala Ala Ala Ala Trp Gly Val Ser Leu Leu Leu Gly Leu Leu Pro Ala
 260 265 270
 25 Leu Gly Trp Asn Cys Leu Gly Arg Leu Asp Ala Cys Ser Thr Val Leu
 275 280 285
 Pro Leu Tyr Ala Lys Ala Tyr Val Leu Phe Cys Val Leu Ala Phe Val
 290 295 300
 30 Gly Ile Leu Ala Ala Ile Cys Ala Leu Tyr Ala Arg Ile Tyr Cys Gln
 305 310 315 320
 Val Arg Ala Asn Ala Arg Arg Leu Pro Ala Arg Pro Gly Thr Ala Gly
 325 330 335
 Thr Thr Ser Thr Arg Ala Arg Arg Lys Pro Arg Ser Leu Ala Leu Leu
 340 345 350
 35 Arg Thr Leu Ser Val Val Leu Leu Ala Phe Val Ala Cys Trp Gly Pro
 355 360 365
 Leu Phe Leu Leu Leu Leu Leu Asp Val Ala Cys Pro Ala Arg Thr Cys

- 39 -

	370		375		380
	Pro Val Leu Leu Gln Ala Asp Pro Phe Leu Gly Leu Ala Met Ala Asn				
	385		390		395 400
5	Ser Leu Leu Asn Pro Ile Ile Tyr Thr Leu Thr Asn Arg Asp Leu Arg				
		405		410	415
	His Ala Leu Leu Arg Leu Val Cys Cys Gly Arg His Ser Cys Gly Arg				
		420		425	430
	Asp Pro Ser Gly Ser Gln Gln Ser Ala Ser Ala Ala Glu Ala Ser Gly				
		435		440	445
10	Gly Leu Arg Arg Cys Leu Pro Pro Gly Leu Asp Gly Ser Phe Ser Gly				
		450		455	460
	Ser Glu Arg Ser Ser Pro Gln Arg Asp Gly Leu Asp Thr Ser Gly Ser				
		465		470	475 480
15	Thr Gly Ser Pro Gly Ala Pro Thr Ala Ala Arg Thr Leu Val Ser Glu				
		485		490	495
	Pro Ala Ala Asp				
		500			

(32) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 1029 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

ATGCAAGCCG TCGACAATCT CACCTCTGCG CCTGGGAACA CCAGTCTGTG CACCAGAGAC 60
 TACAAAATCA CCCAGGTCCT CTTCCCACTG CTCTACACTG TCCTGTTTTT TGTGGGACTT 120
 ATCACAAATG GCCTGGCGAT GAGGATTTTC TTTCAAATCC GGAGTAAATC AAACCTTTATT 180
 ATTTTCTTA AGAACACAGT CATTTCTGAT CTTCTCATGA TTCTGACTTT TCCATTCAAA 240
 30 ATTCTTAGTG ATGCCAAACT GGGAAACAGGA CCACTGAGAA CTTTTGTGTG TCAAGTTACC 300
 TCCGTCATAT TTTATTTTAC AATGTATATC AGTATTTTAT TCCTGGGACT GATAACTATC 360
 GATCGCTACC AGAAGACCAC CAGGCCATTT AAAACATCCA ACCCAAAAAA TCTCTTGGGG 420
 GCTAAGATTC TCTCTGTTGT CATCTGGGCA TTCATGTTCT TACTCTCTTT GCCTAACATG 480

- 40 -

ATTCTGACCA ACAGGCAGCC GAGAGACAAG AATGTGAAGA AATGCTCTTT CCTTAAATCA 540
 GAGTTCGGTC TAGTCTGGCA TGAAATAGTA AATTACATCT GTCAAGTCAT TTTCTGGATT 600
 AATTTCTTAA TTGTTATTGT ATGTTATACA CTCATTACAA AAGAACTGTA CCGGTCATAC 660
 GTAAGAACGA GGGGTGTAGG TAAAGTCCCC AGGAAAAAGG TGAACGTCAA AGTTTTTCATT 720
 5 ATCATTGCTG TATTCTTTAT TTGTTTGTGTT CCTTCCATT TTGCCCCAAT TCCTTACACC 780
 CTGAGCCAAA CCCGGGATGT CTTTGACTGC ACTGCTGAAA ATACTCTGTT CTATGTGAAA 840
 GAGAGCACTC TGTGGTTAAC TTCCTTAAAT GCATGCCTGG ATCCGTTCAT CTATTTTTTTC 900
 CTTTGCAAGT CCTTCAGAAA TTCCTTGATA AGTATGCTGA AGTGCCCCAA TTCTGCAACA 960
 TCTCTGTCCC AGGACAATAG GAAAAAAGAA CAGGATGGTG GTGACCCAAA TGAAGAGACT1020
 10 CCAATGTAA 1029

(33) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 342 amino acids
 (B) TYPE: amino acid
 15 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

20 Met Gln Ala Val Asp Asn Leu Thr Ser Ala Pro Gly Asn Thr Ser Leu
 1 5 10 15
 Cys Thr Arg Asp Tyr Lys Ile Thr Gln Val Leu Phe Pro Leu Leu Tyr
 20 25 30
 Thr Val Leu Phe Phe Val Gly Leu Ile Thr Asn Gly Leu Ala Met Arg
 35 40 45
 25 Ile Phe Phe Gln Ile Arg Ser Lys Ser Asn Phe Ile Ile Phe Leu Lys
 50 55 60
 Asn Thr Val Ile Ser Asp Leu Leu Met Ile Leu Thr Phe Pro Phe Lys
 65 70 75 80
 30 Ile Leu Ser Asp Ala Lys Leu Gly Thr Gly Pro Leu Arg Thr Phe Val
 85 90 95
 Cys Gln Val Thr Ser Val Ile Phe Tyr Phe Thr Met Tyr Ile Ser Ile
 100 105 110
 Ser Phe Leu Gly Leu Ile Thr Ile Asp Arg Tyr Gln Lys Thr Thr Arg

- 41 -

	115	120	125
	Pro Phe Lys Thr Ser Asn	Pro Lys Asn Leu Leu Gly	Ala Lys Ile Leu
	130	135	140
5	Ser Val Val Ile Trp Ala Phe Met Phe Leu Leu Ser Leu Pro Asn Met		
	145	150	155 160
	Ile Leu Thr Asn Arg Gln Pro Arg Asp Lys Asn Val Lys Lys Cys Ser		
		165	170 175
	Phe Leu Lys Ser Glu Phe Gly Leu Val Trp His Glu Ile Val Asn Tyr		
		180	185 190
10	Ile Cys Gln Val Ile Phe Trp Ile Asn Phe Leu Ile Val Ile Val Cys		
		195	200 205
	Tyr Thr Leu Ile Thr Lys Glu Leu Tyr Arg Ser Tyr Val Arg Thr Arg		
		210	215 220
15	Gly Val Gly Lys Val Pro Arg Lys Lys Val Asn Val Lys Val Phe Ile		
		225	230 235 240
	Ile Ile Ala Val Phe Phe Ile Cys Phe Val Pro Phe His Phe Ala Arg		
		245	250 255
	Ile Pro Tyr Thr Leu Ser Gln Thr Arg Asp Val Phe Asp Cys Thr Ala		
		260	265 270
20	Glu Asn Thr Leu Phe Tyr Val Lys Glu Ser Thr Leu Trp Leu Thr Ser		
		275	280 285
	Leu Asn Ala Cys Leu Asp Pro Phe Ile Tyr Phe Phe Leu Cys Lys Ser		
		290	295 300
25	Phe Arg Asn Ser Leu Ile Ser Met Leu Lys Cys Pro Asn Ser Ala Thr		
		305	310 315 320
	Ser Leu Ser Gln Asp Asn Arg Lys Lys Glu Gln Asp Gly Gly Asp Pro		
		325	330 335
	Asn Glu Glu Thr Pro Met		
		340	

30 (34) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1077 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 42 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATGTCGGTCT GCTACCGTCC CCCAGGGAAC GAGACACTGC TGAGCTGGAA GACTTCGCGG 60
 GCCACAGGCA CAGCCTTCCT GCTGCTGGCG GCGCTGCTGG GGCTGCCTGG CAACGGCTTC 120
 GTGGTGTGGA GCTTGGCGGG CTGGCGGCCT GCACGGGGGC GACCGCTGGC GGCCACGCTT 180
 5 GTGCTGCACC TGGCGCTGGC CGACGGCGCG GTGCTGCTGC TCACGCCGCT CTTTGTGGCC 240
 TTCCTGACCC GGCAGGCCTG GCCGCTGGGC CAGGCGGGCT GCAAGGCGGT GTACTACGTG 300
 TGC GCGCTCA GCATGTACGC CAGCGTGCTG CTCACCGGCC TGCTCAGCCT GCAGCGCTGC 360
 CTCGAGTCA CCCGCCCTT CCTGGCGCCT CGGCTGCGCA GCGCGGCCCT GGCCCGCCGC 420
 CTGCTGCTGG CGGTCTGGCT GGCCGCCCTG TTGCTCGCCG TCCCGGCCGC CGTCTACCGC 480
 10 CACCTGTGGA GGGACCGCGT ATGCCAGCTG TGCCACCCGT CGCCGGTCCA CGCCGCCGCC 540
 CACCTGAGCC TGGAGACTCT GACCGCTTTC GTGCTTCCTT TCGGGCTGAT GCTCGGCTGC 600
 TACAGCGTGA CGCTGGCAGC GCTGCGGGGC GCGCGCTGGG GCTCCGGGCG GCACGGGGCG 660
 CGGGTGGGCC GGCTGGTGAG CGCCATCGTG CTTGCCTTCG GCTTGCTCTG GGCCCCCTAC 720
 CACGCAGTCA ACCTTCTGCA GCGGGTCGCA GCGCTGGCTC CACCGGAAGG GGCCTTGGCG 780
 15 AAGCTGGGCG GAGCCGGCCA GCGGGCGCGA GCGGGAATA CGGCCTTGGC CTTCTTCAGT 840
 TCTAGCGTCA ACCCGGTGCT CTACGTCTTC ACCGCTGGAG ATCTGCTGCC CCGGGCAGGT 900
 CCCCGTTTCC TCACGCGGCT CTTCAAGGC TCTGGGGAGG CCCGAGGGGG CGGCCGCTCT 960
 AGGGAAGGGA CCATGGAGCT CCGAACTACC CCTCAGCTGA AAGTGGTGGG GCAGGGCCGC 1020
 GGCAATGGAG ACCCGGGGGG TGGGATGGAG AAGGACGGTC CGGAATGGGA CCTTTGA 1077

20 (35) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 358 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

25 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser Trp
 1 5 10 15

30 Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala Ala Leu

- 43 -

	20	25	30
	Leu Gly Leu Pro Gly Asn Gly Phe Val Val Trp Ser Leu Ala Gly Trp		
	35	40	45
5	Arg Pro Ala Arg Gly Arg Pro Leu Ala Ala Thr Leu Val Leu His Leu		
	50	55	60
	Ala Leu Ala Asp Gly Ala Val Leu Leu Leu Thr Pro Leu Phe Val Ala		
	65	70	75 80
	Phe Leu Thr Arg Gln Ala Trp Pro Leu Gly Gln Ala Gly Cys Lys Ala		
		85 90	95
10	Val Tyr Tyr Val Cys Ala Leu Ser Met Tyr Ala Ser Val Leu Leu Thr		
	100	105	110
	Gly Leu Leu Ser Leu Gln Arg Cys Leu Ala Val Thr Arg Pro Phe Leu		
	115	120	125
15	Ala Pro Arg Leu Arg Ser Pro Ala Leu Ala Arg Arg Leu Leu Leu Ala		
	130	135	140
	Val Trp Leu Ala Ala Leu Leu Leu Ala Val Pro Ala Ala Val Tyr Arg		
	145	150	155 160
	His Leu Trp Arg Asp Arg Val Cys Gln Leu Cys His Pro Ser Pro Val		
		165 170	175
20	His Ala Ala Ala His Leu Ser Leu Glu Thr Leu Thr Ala Phe Val Leu		
	180	185	190
	Pro Phe Gly Leu Met Leu Gly Cys Tyr Ser Val Thr Leu Ala Arg Leu		
	195	200	205
25	Arg Gly Ala Arg Trp Gly Ser Gly Arg His Gly Ala Arg Val Gly Arg		
	210	215	220
	Leu Val Ser Ala Ile Val Leu Ala Phe Gly Leu Leu Trp Ala Pro Tyr		
	225	230	235 240
	His Ala Val Asn Leu Leu Gln Ala Val Ala Ala Leu Ala Pro Pro Glu		
		245 250	255
30	Gly Ala Leu Ala Lys Leu Gly Gly Ala Gly Gln Ala Ala Arg Ala Gly		
	260	265	270
	Thr Thr Ala Leu Ala Phe Phe Ser Ser Ser Val Asn Pro Val Leu Tyr		
	275	280	285
35	Val Phe Thr Ala Gly Asp Leu Leu Pro Arg Ala Gly Pro Arg Phe Leu		
	290	295	300
	Thr Arg Leu Phe Glu Gly Ser Gly Glu Ala Arg Gly Gly Gly Arg Ser		
	305	310	315 320

- 44 -

Arg Glu Gly Thr Met Glu Leu Arg Thr Thr Pro Gln Leu Lys Val Val
325 330 335

Gly Gln Gly Arg Gly Asn Gly Asp Pro Gly Gly Gly Met Glu Lys Asp
340 345 350

5 Gly Pro Glu Trp Asp Leu
355

(36) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 1005 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

15 ATGCTGGGGA TCATGGCATG GAATGCAACT TGCAAAACT GGCTGGCAGC AGAGGCTGCC 60
CTGGAAAAGT ACTACCTTTC CATTTTTTAT GGGATTGAGT TCGTTGTGGG AGTCCTTGGA 120
AATACCATTG TTGTTTACGG CTACATCTTC TCTCTGAAGA ACTGGAACAG CAGTAATATT 180
TATCTCTTTA ACCTCTCTGT CTCTGACTTA GCTTTTCTGT GCACCCTCCC CATGCTGATA 240
AGGAGTTATG CCAATGGAAA CTGGATATAT GGAGACGTGC TCTGCATAAG CAACCGATAT 300
20 GTGCTTCATG CCAACCTCTA TACCAGCATT CTCTTTCTCA CTTTATCAG CATAGATCGA 360
TACTTGATAA TTAAGTATCC TTTCCGAGAA CACCTTCTGC AAAAGAAAGA GTTTGCTATT 420
TTAATCTCCT TGGCCATTG GGTTTTAGTA ACCTTAGAGT TACTACCCAT ACTTCCCCTT 480
ATAAATCCTG TTATAACTGA CAATGGCACC ACCTGTAATG ATTTTGCAAG TTCTGGAGAC 540
CCCAACTACA ACCTCATTTA CAGCATGTGT CTAACACTGT TGGGGTTCCT TATTCCTCTT 600
25 TTTGTGATGT GTTTCTTTTA TTACAAGATT GCTCTCTTCC TAAAGCAGAG GAATAGGCAG 660
GTTGCTACTG CTCTGCCCCT TGAAAAGCCT CTCAACTTGG TCATCATGGC AGTGGTAATC 720
TTCTCTGTGC TTTTACACC CTATCACGTC ATGCGGAATG TGAGGATCGC TTCACGCCTG 780
GGGAGTTGGA AGCAGTATCA GTGCACTCAG GTCGTCATCA ACTCCTTTTA CATTGTGACA 840
CGGCCTTTGG CCTTTCTGAA CAGTGTATC AACCTGTCT TCTATTTTCT TTTGGGAGAT 900
30 CACTTCAGGG ACATGCTGAT GAATCAACTG AGACACAACT TCAAATCCCT TACATCCTTT 960
AGCAGATGGG CTCATGAACT CCTACTTTCA TTCAGAGAAA AGTGA 1005

- 45 -

(37) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 334 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

10 Met Leu Gly Ile Met Ala Trp Asn Ala Thr Cys Lys Asn Trp Leu Ala
 1 5 10 15
 Ala Glu Ala Ala Leu Glu Lys Tyr Tyr Leu Ser Ile Phe Tyr Gly Ile
 20 25 30
 Glu Phe Val Val Gly Val Leu Gly Asn Thr Ile Val Val Tyr Gly Tyr
 35 40 45
 15 Ile Phe Ser Leu Lys Asn Trp Asn Ser Ser Asn Ile Tyr Leu Phe Asn
 50 55 60
 Leu Ser Val Ser Asp Leu Ala Phe Leu Cys Thr Leu Pro Met Leu Ile
 65 70 75 80
 20 Arg Ser Tyr Ala Asn Gly Asn Trp Ile Tyr Gly Asp Val Leu Cys Ile
 85 90 95
 Ser Asn Arg Tyr Val Leu His Ala Asn Leu Tyr Thr Ser Ile Leu Phe
 100 105 110
 Leu Thr Phe Ile Ser Ile Asp Arg Tyr Leu Ile Ile Lys Tyr Pro Phe
 115 120 125
 25 Arg Glu His Leu Leu Gln Lys Lys Glu Phe Ala Ile Leu Ile Ser Leu
 130 135 140
 Ala Ile Trp Val Leu Val Thr Leu Glu Leu Leu Pro Ile Leu Pro Leu
 145 150 155 160
 30 Ile Asn Pro Val Ile Thr Asp Asn Gly Thr Thr Cys Asn Asp Phe Ala
 165 170 175
 Ser Ser Gly Asp Pro Asn Tyr Asn Leu Ile Tyr Ser Met Cys Leu Thr
 180 185 190
 Leu Leu Gly Phe Leu Ile Pro Leu Phe Val Met Cys Phe Phe Tyr Tyr
 195 200 205
 35 Lys Ile Ala Leu Phe Leu Lys Gln Arg Asn Arg Gln Val Ala Thr Ala
 210 215 220

- 46 -

Leu Pro Leu Glu Lys Pro Leu Asn Leu Val Ile Met Ala Val Val Ile
 225 230 235 240
 Phe Ser Val Leu Phe Thr Pro Tyr His Val Met Arg Asn Val Arg Ile
 245 250 255
 5 Ala Ser Arg Leu Gly Ser Trp Lys Gln Tyr Gln Cys Thr Gln Val Val
 260 265 270
 Ile Asn Ser Phe Tyr Ile Val Thr Arg Pro Leu Ala Phe Leu Asn Ser
 275 280 285
 10 Val Ile Asn Pro Val Phe Tyr Phe Leu Leu Gly Asp His Phe Arg Asp
 290 295 300
 Met Leu Met Asn Gln Leu Arg His Asn Phe Lys Ser Leu Thr Ser Phe
 305 310 315 320
 Ser Arg Trp Ala His Glu Leu Leu Leu Ser Phe Arg Glu Lys
 325 330

15 (38) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1296 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

ATGCAGGCGC TTAACATTAC CCCGGAGCAG TTCTCTCGGC TGCTGCGGGA CCACAACCTG 60
 ACGCGGGAGC AGTTCATCGC TCTGTACCGG CTGCGACCGC TCGTCTACAC CCCAGAGCTG 120
 25 CCGGGACGCG CCAAGCTGGC CCTCGTGCTC ACCGGCGTGC TCATCTTCGC CCTGGCGCTC 180
 TTTGGCAATG CTCTGGTGTT CTACGTGGTG ACCCGCAGCA AGGCCATGCG CACCGTCACC 240
 AACATCTTTA TCTGCTCCTT GCGGCTCAGT GACCTGCTCA TCACCTTCTT CTGCATTCCC 300
 GTCACCATGC TCCAGAACAT TTCCGACAAC TGGCTGGGGG GTGCTTTCAT TTGCAAGATG 360
 GTGCCATTTG TCCAGTCTAC CGCTGTTGTG ACAGAAATGC TCACTATGAC CTGCATTGCT 420
 30 GTGGAAAGGC ACCAGGGACT TGTGCATCCT TTAAAAATGA AGTGGCAATA CACCAACCGA 480
 AGGGCTTTCA CAATGCTAGG TGTGGTCTGG CTGGTGGCAG TCATCGTAGG ATCACCCTATG 540
 TGGCACGTGC AACAACTTGA GATCAAATAT GACTTCCTAT ATGAAAAGGA ACACATCTGC 600
 TGCTTAGAAG AGTGGACCAG CCCTGTGCAC CAGAAGATCT ACACCACCTT CATCCTTGTC 660

- 47 -

ATCCTCTTCC TCCTGCCTCT TATGGTGATG CTTATTCTGT ACAGTAAAT TGTTATGAA 720
 CTTTGGATAA AGAAAAGAGT TGGGGATGGT TCAGTGCTTC GAACTATTCA TGGAAAAGAA 780
 ATGTCCAAAA TAGCCAGGAA GAAGAAACGA GCTGTCATTA TGATGGTGAC AGTGGTGGCT 840
 CTCTTTGCTG TGTGCTGGGC ACCATTCCAT GTTGTCCATA TGATGATTGA ATACAGTAAT 900
 5 TTTGAAAAGG AATATGATGA TGTCACAATC AAGATGATTT TTGCTATCGT GCAAATTATT 960
 GGATTTTCCA ACTCCATCTG TAATCCCATT GTCTATGCAT TTATGAATGA AACTTCAAA1020
 AAAAAATGTTT TGTCTGCAGT TTGTTATTGC ATAGTAAATA AAACCTTCTC TCCAGCACAA1080
 AGGCATGGAA ATTCAGGAAT TACAATGATG CGGAAGAAAG CAAAGTTTTC CCTCAGAGAG1140
 AATCCAGTGG AGGAAACCAA AGGAGAAGCA TTCAGTGATG GCAACATTGA AGTCAAATTG1200
 10 TGTGAACAGA CAGAGGAGAA GAAAAAGCTC AAACGACATC TTGCTCTCTT TAGGTCTGAA1260
 CTGGCTGAGA ATTCTCCTTT AGACAGTGGG CATTAA 1296

(39) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 431 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

20 Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg
 1 5 10 15
 Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg
 20 25 30
 25 Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu
 35 40 45
 Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala
 50 55 60
 Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr
 65 70 75 80
 30 Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe
 85 90 95
 Phe Cys Ile Pro Val Thr Met Leu Gln Asn Ile Ser Asp Asn Trp Leu

- 48 -

	100	105	110
	Gly Gly Ala Phe Ile Cys Lys Met Val Pro Phe Val Gln Ser Thr Ala		
	115	120	125
5	Val Val Thr Glu Met Leu Thr Met Thr Cys Ile Ala Val Glu Arg His		
	130	135	140
	Gln Gly Leu Val His Pro Phe Lys Met Lys Trp Gln Tyr Thr Asn Arg		
	145	150	155 160
	Arg Ala Phe Thr Met Leu Gly Val Val Trp Leu Val Ala Val Ile Val		
	165	170	175
10	Gly Ser Pro Met Trp His Val Gln Gln Leu Glu Ile Lys Tyr Asp Phe		
	180	185	190
	Leu Tyr Glu Lys Glu His Ile Cys Cys Leu Glu Glu Trp Thr Ser Pro		
	195	200	205
15	Val His Gln Lys Ile Tyr Thr Thr Phe Ile Leu Val Ile Leu Phe Leu		
	210	215	220
	Leu Pro Leu Met Val Met Leu Ile Leu Tyr Ser Lys Ile Gly Tyr Glu		
	225	230	235 240
	Leu Trp Ile Lys Lys Arg Val Gly Asp Gly Ser Val Leu Arg Thr Ile		
	245	250	255
20	His Gly Lys Glu Met Ser Lys Ile Ala Arg Lys Lys Lys Arg Ala Val		
	260	265	270
	Ile Met Met Val Thr Val Val Ala Leu Phe Ala Val Cys Trp Ala Pro		
	275	280	285
25	Phe His Val Val His Met Met Ile Glu Tyr Ser Asn Phe Glu Lys Glu		
	290	295	300
	Tyr Asp Asp Val Thr Ile Lys Met Ile Phe Ala Ile Val Gln Ile Ile		
	305	310	315 320
	Gly Phe Ser Asn Ser Ile Cys Asn Pro Ile Val Tyr Ala Phe Met Asn		
	325	330	335
30	Glu Asn Phe Lys Lys Asn Val Leu Ser Ala Val Cys Tyr Cys Ile Val		
	340	345	350
	Asn Lys Thr Phe Ser Pro Ala Gln Arg His Gly Asn Ser Gly Ile Thr		
	355	360	365
35	Met Met Arg Lys Lys Ala Lys Phe Ser Leu Arg Glu Asn Pro Val Glu		
	370	375	380
	Glu Thr Lys Gly Glu Ala Phe Ser Asp Gly Asn Ile Glu Val Lys Leu		
	385	390	395 400

- 49 -

Cys Glu Gln Thr Glu Glu Lys Lys Lys Leu Lys Arg His Leu Ala Leu
405 410 415

Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His
420 425 430

5 (40) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTGTGTACAG CAGTTCGCAG AGTG

24

(41) INFORMATION FOR SEQ ID NO:40:

15 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAGTGCCAGG CAGAGCAGGT AGAC

24

(42) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CCCGAATTCC TGCTTGCTCC CAGCTTGGCC C

31

(43) INFORMATION FOR SEQ ID NO:42:

- 50 -

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 32 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGTGGATCCT GCTGTCAAAG GTCCCATTCG GG

32

10 (44) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TCACAATGCT AGGTGTGGTC

20

20 (45) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TGCATAGACA ATGGGATTAC AG

22

30 (46) INFORMATION FOR SEQ ID NO:45:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 511 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

- 51 -

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TCACAATGCT AGGTGTGGTC TGGCTGGTGG CAGTCATCGT AGGATCACCC ATGTGGCACC 60
5 TGCAACAAC T GAGATCAAA TATGACTTCC TATATGAAAA GGAACACATC TGCTGCTTAG 120
AAGAGTGGAC CAGCCCTGTG CACCAGAAGA TCTACACCAC CTTCATCCTT GTCATCCTCT 180
TCCTCCTGCC TCTTATGGTG ATGCTTATTC TGTACGTAAA ATTGGTTATG AACTTTGGAT 240
AAAGAAAAGA GTTGGGGATG GTTCAGTGCT TCGAACTATT CATGGAAAAG AAATGTCCAA 300
AATAGCCAGG AAGAAGAAAC GAGCTGTCAT TATGATGGTG ACAGTGGTGG CTCTCTTTGC 360
10 TGTGTGCTGG GCACCATTCC ATGTTGTCCA TATGATGATT GAATACAGTA ATTTTGAAAA 420
GGAATATGAT GATGTCACAA TCAAGATGAT TTTTGCTATC GTGCAAATTA TTGGATTTTC 480
CAACTCCATC TGTAATCCCA TTGTCTATGC A 511

(47) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CTGCTTAGAA GAGTGGACCA G

21

(48) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (iv) ANTI-SENSE: NO

- 52 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CTGTGCACCA GAAGATCTAC AC

22

(49) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CAAGGATGAA GGTGGTGTAG A

21

(50) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GTGTAGATCT TCTGGTGCAC AGG

23

(51) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GCAATGCAGG TCATAGTGAG C

21

(52) INFORMATION FOR SEQ ID NO:51:

- 53 -

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 27 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

10 TGGAGCATGG TGACGGGAAT GCAGAAG

27

(53) INFORMATION FOR SEQ ID NO:52:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 27 base pairs
 (B) TYPE: nucleic acid
15 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

20 GTGATGAGCA GGTCACTGAG CGCCAAG

27

(54) INFORMATION FOR SEQ ID NO:53:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 23 base pairs
 (B) TYPE: nucleic acid
25 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

30 GCAATGCAGG CGCTTAACAT TAC

23

(55) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 22 base pairs

- 54 -

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TTGGGTTACA ATCTGAAGGG CA

22

(56) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- 10
- (A) LENGTH: 23 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

ACTCCGTGTC CAGCAGGACT CTG

23

(57) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- 20
- (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TGCGTGTTCC TGGACCCTCA CGTG

24

(58) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- 30
- (A) LENGTH: 29 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- 55 -

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CAGGCCTTGG ATTTTAATGT CAGGGATGG

29

5 (59) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GGAGAGTCAG CTCTGAAAGA ATTCAGG

27

15 (60) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TGATGTGATG CCAGATACTA ATAGCAC

27

25 (61) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

- 56 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

CCTGATTCAT TTAGGTGAGA TTGAGAC

27

(62) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GACAGGTACC TTGCCATCAA G

21

(63) INFORMATION FOR SEQ ID NO:62:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

20 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTGCACAATG CCAGTGATAA GG

22

(64) INFORMATION FOR SEQ ID NO:63:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

30 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CTGACTTCTT GTTCCTGGCA GCAGCGG

27

- 57 -

(65) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 27 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

10 AGACCAGCCA GGGCAGCTG AAGAGTG

27

(66) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 32 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

20 GATCAAGCTT CCATCCTACT GAAACCATGG TC

32

(67) INFORMATION FOR SEQ ID NO:66:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 35 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

30 GATCAGATCT CAGTTCCAAT ATTCACACCA CCGTC

35

(68) INFORMATION FOR SEQ ID NO:67:

- (i) SEQUENCE CHARACTERISTICS:

- 58 -

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

CTGGTGTGCT CCATGGCATC CC

22

(69) INFORMATION FOR SEQ ID NO:68:

- 10 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GTAAGCCTCC CAGAACGAGA GG

22

(70) INFORMATION FOR SEQ ID NO:69:

- 20 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CAGCGCAGGG TGAAGCCTGA GAGC

24

(71) INFORMATION FOR SEQ ID NO:70:

- 30 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- 59 -

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GGCACCTGCT GTGACCTGTG CAGG

24

5 (72) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

GTCCTGCCAC TTCGAGACAT GG

22

15 (73) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GAAACTTCTC TGCCCTTACC GTC

23

25 (74) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

- 60 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

CCAACACCAG CATCCATGGC ATCAAG

26

(75) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

GGAGAGTCAG CTCTGAAAGA ATTCAGG

27

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, C07K 14/72	A3	(11) International Publication Number: WO 00/31258
		(43) International Publication Date: 2 June 2000 (02.06.00)

(21) International Application Number: PCT/US99/23687

(22) International Filing Date: 13 October 1999 (13.10.99)

(30) Priority Data:

60/109,213	20 November 1998 (20.11.98)	US
60/120,416	16 February 1999 (16.02.99)	US
60/121,852	26 February 1999 (26.02.99)	US
60/123,946	12 March 1999 (12.03.99)	US
60/123,949	12 March 1999 (12.03.99)	US
60/136,436	28 May 1999 (28.05.99)	US
60/136,437	28 May 1999 (28.05.99)	US
60/136,439	28 May 1999 (28.05.99)	US
60/136,567	28 May 1999 (28.05.99)	US
60/137,127	28 May 1999 (28.05.99)	US
60/137,131	28 May 1999 (28.05.99)	US
60/141,448	29 June 1999 (29.06.99)	US
60/156,653	29 September 1999 (29.09.99)	US
60/156,633	29 September 1999 (29.09.99)	US
60/156,555	29 September 1999 (29.09.99)	US
60/156,634	29 September 1999 (29.09.99)	US
60/157,280	1 October 1999 (01.10.99)	US
60/157,294	1 October 1999 (01.10.99)	US
60/157,281	1 October 1999 (01.10.99)	US
60/157,293	1 October 1999 (01.10.99)	US
60/157,282	1 October 1999 (01.10.99)	US
09/417,044	12 October 1999 (12.10.99)	US
09/416,760	12 October 1999 (12.10.99)	US

(71) Applicant (for all designated States except US): ARENA PHARMACEUTICALS, INC. [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CHEN, Ruoping [CN/US]; 5296 Timber Branch Way, San Diego, CA 92130 (US). DANG, Huong, T. [US/US]; 5352 Oak Park Drive, San Diego, CA 92105 (US). LIAW, Chen, W. [US/US]; 7668 Salix Place, San Diego, CA 92129 (US). LIN, I-Lin [-/US]; 8291-7 Gold Coast Drive, San Diego, CA 92126 (US).

(74) Agents: MILLER, Suzanne, E. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris LLP, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(88) Date of publication of the international search report:
5 October 2000 (05.10.00)

(54) Title: HUMAN ORPHAN G PROTEIN-COUPLED RECEPTORS

(57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to endogenous, human orphan G protein-coupled receptors.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23687

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILLIAMS S.: "Human DNA sequence from clone 417022 on chromosome 6q16.1-16.3." EMBL DATABASE ENTRY HS417022, 3 November 1998 (1998-11-03), XP002136831 page 1 -page 2 nts. 105786 - 107045	1-4
P, X	WO 99 24569 A (ONO PHARMACEUTICAL CO ;HAGA HISANORI (JP); NAKADE SHINJI (JP); FUK) 20 May 1999 (1999-05-20) SEQ.ID.3 --- -/--	1-4

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

14 July 2000

Date of mailing of the international search report

02.08.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo.nl,
Fax: (+31-70) 340-3016

Authorized officer

Mandl, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STADEL J. M. ET AL.: "Orphan G protein-coupled receptors: A neglected opportunity for pioneer drug discovery." TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 18, no. 11, November 1997 (1997-11), pages 430-437, XP002073279 ISSN: 0165-6147 the whole document	1-4
E	WO 00 23588 A (WEICH NADINE S ;GLUCKSMANN MARIA ALEXANDRA (US); MILLENNIUM PHARM) 27 April 2000 (2000-04-27) SEQ.IDs. 5 and 6	5-8
P, X	MUZNY D. ET AL.: "Homo sapiens chromosome 2p13.3, clone RPC111-433J6 - sequencing in progress - 100 unordered pieces." EMBL DATABASE ACCESSION NUMBER AC006087, 7 December 1998 (1998-12-07), XP002136323 nts. 133160-134279	5
X	SMITH D.R.: "Sequencing of human chromosome 10." EMBL DATABASE ACCESSION NUMBER AC005849, 22 October 1998 (1998-10-22), XP002142585 nts. 111594-113007	17
E	WO 99 55732 A (AHMAD SULTAN ;CAO JACK (CA); DONNELL DAJAN O (CA); WALKER PHILIPPE) 4 November 1999 (1999-11-04) the whole document	21-24
X	O'DOWD B. F. ET AL.: "DISCOVERY OF THREE NOVEL G-PROTEIN-COUPLED RECEPTOR GENES" GENOMICS, vol. 47, no. 2, 15 January 1998 (1998-01-15), pages 310-313, XP000863786 ISSN: 0888-7543 the whole document	29-32
P, X	WO 99 46378 A (MATSUMOTO MITSUYUKI ;SAITO TETSU (JP); SUGIMOTO TORU (JP); TAKASAKI) 16 September 1999 (1999-09-16) SEQ.ID.1, SEQ.ID.3, SEQ.ID.5	29-32, 37-40, 49-52
X	STRAUSBERG R.: "National Cancer Institute, Cancer Genome Anatomy Project." EMBL DATABASE ACCESSION NUMBER AI090920, 19 August 1998 (1998-08-19), XP002142586 abstract	33

-/-

INTERNATIONAL SEARCH REPORT

Int'l. Application No

PCT/US 99/23687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 39441 A (INCYTE PHARMA INC ;AU YOUNG JANICE (US); CHENG MUZONG (US); GUEGLE) 11 September 1998 (1998-09-11) the whole document ---	33-36
P,X	EP 0 913 471 A (SMITHKLINE BEECHAM CORP) 6 May 1999 (1999-05-06) the whole document ---	33-36
E	WO 99 55733 A (SMITHKLINE BEECHAM CORP) 4 November 1999 (1999-11-04) the whole document ---	37-40
X	MATSUOKA I. ET AL.: "Identification of novel members of G-protein coupled receptor subfamily" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 194, no. 1, 15 July 1993 (1993-07-15), pages 504-511, XP002102959 ISSN: 0006-291X the whole document ---	41-44
X	HILLIER L. ET AL.: "Generation and analysis of 280000 human expressed sequence tags." EMBL DATABASE ACCESSION NUMBER H67224, 21 October 1995 (1995-10-21), XP002142587 abstract ---	41
X	STRAUSBERG R.: "National Cancer Institute, Cancer Genome Project." EMBL DATABASE ACCESSION NUMBER AI131555, 23 September 1998 (1998-09-23), XP002142588 abstract ---	41
P,X	WO 99 24463 A (INCYTE PHARMA INC ;MATHUR PREETE (US); REDDY ROOPA (US); AU YOUNG) 20 May 1999 (1999-05-20) SEQ.IDs. 16 and 17 ---	41-44
P,X	EP 0 899 332 A (SMITHKLINE BEECHAM CORP) 3 March 1999 (1999-03-03) the whole document ---	41-44
E	WO 00 26369 A (CHIRON CORP ;KHOJA HAMIDUDDIN (US); SHYMALA VENKATAKRISHNA (US)) 11 May 2000 (2000-05-11) the whole document ---	41-44
E	WO 99 52945 A (MILLENNIUM PHARM INC) 21 October 1999 (1999-10-21) figure 2; example 2 ---	41-44

INTERNATIONAL SEARCH REPORT

Inte. onal Application No

PCT/US 99/23687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WENG ET AL.: "A DNA damage and stress inducible G protein-coupled receptor blocks cells in G2/M" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 95, 1 October 1998 (1998-10-01), pages 12334-12339, XP002095309 ISSN: 0027-8424 the whole document	45-48
X	WO 98 31810 A (SCHERING CORP) 23 July 1998 (1998-07-23) SEQ.IDs. 7 and 8	45-48
X	EP 0 860 502 A (SMITHKLINE BEECHAM CORP) 26 August 1998 (1998-08-26) the whole document	45-48
P, X	WO 99 25830 A (UNIV CALIFORNIA) 27 May 1999 (1999-05-27) the whole document	45-48
E	WO 99 55734 A (SMITHKLINE BEECHAM CORP) 4 November 1999 (1999-11-04) the whole document	49-52
E	WO 00 12707 A (MILLENNIUM PHARM INC) 9 March 2000 (2000-03-09) the whole document	49-52
X	STRAUSBERG R. : "National Cancer Institute, Cancer Genome Anatomy Project." EMBL DATABASE ACCESSION NUMBER AA804531, 16 February 1998 (1998-02-16), XP002142589 abstract	53
E	WO 00 11170 A (MILLENNIUM PHARM INC) 2 March 2000 (2000-03-02) the whole document	53-56
E	WO 00 11166 A (MILLENNIUM PHARM INC) 2 March 2000 (2000-03-02) the whole document	57-60
X	WO 98 50549 A (HUMAN GENOME SCIENCES INC ; LI YI (US); RUBEN STEVEN M (US)) 12 November 1998 (1998-11-12) SEQ.IDs. 1 and 2	61-64
E	WO 00 28028 A (GU WEI ; WEICH NADINE S (US); GLUCKSMANN MARIA ALEXANDRA (US); MILL) 18 May 2000 (2000-05-18) SEQ.IDs. 1 and 2	61-64
	--- -/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23687

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 42484 A (SMITHKLINE BEECHAM CORP) 26 August 1999 (1999-08-26) SEQ.IDs. 1 and 2 ----	65-68
X	WO 97 20045 A (COR THERAPEUTICS INC) 5 June 1997 (1997-06-05) the whole document ----	69-72
X	WO 97 24929 A (HUMAN GENOME SCIENCES INC) 17 July 1997 (1997-07-17) the whole document ----	69-72
E	WO 00 11015 A (ALPHAGENE INC) 2 March 2000 (2000-03-02) SEQ.IDs. 25 and 26 -----	73-76

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/23687

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4

Human G protein-coupled receptor as characterized by SEQ.ID.2, a cDNA encoding said receptor as characterized by SEQ.ID.1, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

2. Claims: 5-8

Human G protein-coupled receptor as characterized by SEQ.ID.4, a cDNA encoding said receptor as characterized by SEQ.ID.3, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

3. Claims: 9-12

Human G protein-coupled receptor as characterized by SEQ.ID.6, a cDNA encoding said receptor as characterized by SEQ.ID.5, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

4. Claims: 13-16

Human G protein-coupled receptor as characterized by SEQ.ID.8, a cDNA encoding said receptor as characterized by SEQ.ID.7, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

5. Claims: 17-20

Human G protein-coupled receptor as characterized by SEQ.ID.10, a cDNA encoding said receptor as characterized by SEQ.ID.9, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

6. Claims: 21-24

Human G protein-coupled receptor as characterized by SEQ.ID.12, a cDNA encoding said receptor as characterized by SEQ.ID.11, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

7. Claims: 25-28

Human G protein-coupled receptor as characterized by SEQ.ID.14, a cDNA encoding said receptor as characterized by

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SEQ.ID.13, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

8. Claims: 29-32

Human G protein-coupled receptor as characterized by SEQ.ID.16, a cDNA encoding said receptor as characterized by SEQ.ID.15, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

9. Claims: 33-36

Human G protein-coupled receptor as characterized by SEQ.ID.18, a cDNA encoding said receptor as characterized by SEQ.ID.17, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

10. Claims: 37-40

Human G protein-coupled receptor as characterized by SEQ.ID.20, a cDNA encoding said receptor as characterized by SEQ.ID.19, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

11. Claims: 41-44

Human G protein-coupled receptor as characterized by SEQ.ID.22, a cDNA encoding said receptor as characterized by SEQ.ID.21, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

12. Claims: 45-48

Human G protein-coupled receptor as characterized by SEQ.ID.24, a cDNA encoding said receptor as characterized by SEQ.ID.23, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

13. Claims: 49-52

Human G protein-coupled receptor as characterized by SEQ.ID.26, a cDNA encoding said receptor as characterized by SEQ.ID.25, a plasmid comprising said cDNA, and a host cell comprising said plasmid.

14. Claims: 53-56

Human G protein-coupled receptor as characterized by

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SEQ.ID.28, a cDNA encoding said receptor as characterized by
SEQ.ID.27, a plasmid comprising said cDNA, and a host cell
comprising said plasmid.

15. Claims: 57-60

Human G protein-coupled receptor as characterized by
SEQ.ID.30, a cDNA encoding said receptor as characterized by
SEQ.ID.29, a plasmid comprising said cDNA, and a host cell
comprising said plasmid.

16. Claims: 61-64

Human G protein-coupled receptor as characterized by
SEQ.ID.32, a cDNA encoding said receptor as characterized by
SEQ.ID.31, a plasmid comprising said cDNA, and a host cell
comprising said plasmid.

17. Claims: 65-68

Human G protein-coupled receptor as characterized by
SEQ.ID.34, a cDNA encoding said receptor as characterized by
SEQ.ID.33, a plasmid comprising said cDNA, and a host cell
comprising said plasmid.

18. Claims: 69-72

Human G protein-coupled receptor as characterized by
SEQ.ID.36, a cDNA encoding said receptor as characterized by
SEQ.ID.35, a plasmid comprising said cDNA, and a host cell
comprising said plasmid.

19. Claims: 73-76

Human G protein-coupled receptor as characterized by
SEQ.ID.38, a cDNA encoding said receptor as characterized by
SEQ.ID.37, a plasmid comprising said cDNA, and a host cell
comprising said plasmid.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/23687

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9924569	A	20-05-1999	NONE	
WO 0023588	A	27-04-2000	NONE	
WO 9955732	A	04-11-1999	AU 4298099 A	16-11-1999
WO 9946378	A	16-09-1999	AU 3276699 A	27-09-1999
WO 9839441	A	11-09-1998	US 5955303 A AU 6447998 A EP 0973891 A	21-09-1999 22-09-1998 26-01-2000
EP 0913471	A	06-05-1999	CA 2239255 A JP 11235184 A	23-04-1999 31-08-1999
WO 9955733	A	04-11-1999	NONE	
WO 9924463	A	20-05-1999	US 5932445 A AU 1309599 A	03-08-1999 31-05-1999
EP 0899332	A	03-03-1999	CA 2224096 A JP 11056377 A	15-02-1999 02-03-1999
WO 0026369	A	11-05-2000	NONE	
WO 9952945	A	21-10-1999	AU 3749499 A	01-11-1999
WO 9831810	A	23-07-1998	AU 6017098 A	07-08-1998
EP 0860502	A	26-08-1998	CA 2220855 A JP 11028093 A	24-08-1998 02-02-1999
WO 9925830	A	27-05-1999	AU 1402899 A	07-06-1999
WO 9955734	A	04-11-1999	US 6071722 A	06-06-2000
WO 0012707	A	09-03-2000	AU 5801099 A	21-03-2000
WO 0011170	A	02-03-2000	AU 5578699 A	14-03-2000
WO 0011166	A	02-03-2000	AU 5575299 A	14-03-2000
WO 9850549	A	12-11-1998	US 6060272 A EP 1007670 A	09-05-2000 14-06-2000
WO 0028028	A	18-05-2000	NONE	
WO 9942484	A	26-08-1999	NONE	
WO 9720045	A	05-06-1997	US 5871963 A AU 1075397 A CA 2237937 A EP 0868510 A JP 2000500658 T US 6063582 A	16-02-1999 19-06-1997 05-06-1997 07-10-1998 25-01-2000 16-05-2000
WO 9724929	A	17-07-1997	AU 4753496 A CA 2242910 A	01-08-1997 17-07-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23687

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9724929 A		EP 0955808 A	17-11-1999
WO 0011015 A	02-03-2000	AU 5784799 A	14-03-2000

